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Patent- og Varemærkestyrelsen
Kongeriget Danmark

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Head Clerk

TITLE

Substituted Imidazoles, their Preparation and Use

FIELD OF THE INVENTION

The present invention relates to novel substituted imidazoles, to the use of these compounds as medicaments, to pharmaceutical compositions comprising the compounds, and to a method of treatment employing these compounds and compositions. The present compounds show a high and selective binding affinity to the histamine H3 receptor indicating a histamine H3 receptor antagonistic or agonistic activity. As a result, the compounds are useful for the treatment of disorders related to the histamine H3 receptor. More particularly, the present compounds possess a histamine H3 receptor antagonistic activity and are accordingly useful in the treatment of disorders in which a histamine H3 receptor blockade is beneficial.

BACKGROUND OF THE INVENTION

The histamine H3 receptor is known and of current interest for the development of new medicaments (see e.g. Stark, H.; Schlicker, E.; Schunack, W., *Drugs Fut.* **1996**, *21*, 507-520; Leurs, R.; Timmerman, H.; Vollinga, R. C., *Progress in Drug Research* **1995**, *45*, 107-165). The histamine H3 receptor is a presynaptic autoreceptor located in both the central and the peripheral nervous system, the skin and in organs such as the lung, the intestine, probably the spleen and the gastrointestinal tract. The histamine H3 receptor has been demonstrated to regulate the release of histamine and also of other neurotransmitters such as serotonine and acetylcholine. A histamine H3 receptor antagonist would therefore be expected to increase the release of these neurotransmitters in the brain. A histamine H3 receptor agonist, on the contrary, leads to an inhibition of the biosynthesis and release of histamine and also of other neurotransmitters such as serotonine and acetylcholine. These findings suggest that histamine H3 receptor agonists and antagonists could be important mediators of

neuronal activity. Accordingly, the histamine H3 receptor is an important target for new therapeutics.

Imidazoles similar to the compounds of the present invention have previously been prepared, and their biological properties have been investigated (see e.g. Patent, Soc. Farm. Italia S.p.A., FR 2 337 726, 1977, DE 2700012, **1977**, *Chem. Abstr.*, 87, 201535; Hepp, M.; Schunack, W., *Arch. Pharm. (Weinheim Ger.)*, 313, 9, **1980**, 756-762; Vitali et al., *Farmaco Ed. Sci.*, 22, **1967**, 821; Habermehl; Ecsy, *Heterocycles*, 5, **1976**, 127; Arcari, G.; Bernardi, L.; Cimaschi, R.; Falconi, G.; Luini, F.; Scarponi, U., *Arzneim. Forsch.*, 34, 11, **1984**, 1467-1471; Vitali; Bertaccini, *Gazz. Chim. Ital.*, 94, **1964**, 296; Emmett, J. C.; Durant, G. J.; Ganellin, C. R.; Roe, A. M.; Turner, J. L., *J. Med. Chem.*, 25, 10, **1982**, 1168-1174; Nagarajan, K. et al., *Indian J. Chem. Sect. B*, 15, **1977**, 629-634; Casella, L.; Gullotti, M., *J. Am. Chem. Soc.*, 103, 21, **1981**, 6338-6347; Piper, I. M.; MacLean, D. B.; Kvarnstroem, I.; Szarek, W. A., *Can. J. Chem.*, 61, **1983**, 2721-2728; Williams, R. L.; Neergaard, S., *J. Pharm. Sci.*, 71, 1, **1982**, 119-120). Furthermore, EP 589 665, EP 531 874, WO 92/18115, EP 449 521, US 5,091,390, DE 33 02 125 and DE 33 02 126 disclose imidazopyridine derivatives which are stated to be useful either as intermediates or as therapeutically active substances such as angiotensin II antagonists effective to treat hypertension, peripheral kappa opioid receptor activating substances effective to treat inflammatory pain and N-myristoyl transferase inhibitors effective as anti-cancer agents. However, these references neither disclose nor suggest that the imidazoles may have a histamine H3 receptor antagonistic or agonistic activity.

Several publications disclose the preparation and use of histamine H3 agonists and antagonists. Thus, US 4,767,778 (corresponding to EP 214 058), EP 338 939, WO 93/14070, EP 531 219, EP 458 661, EP 197 840, EP 494 010, WO 91/17146, WO 93/12108, WO 93/12107, WO 93/12093, US 5,578,616 (corresponding to WO 95/14007), WO 96/38142, WO 96/38141, WO 95/11894, WO 93/20061, WO 96/40126, WO 95/06037, WO 92/15567 and WO 94/17058 disclose imidazole

derivatives having histamine H3 receptor agonistic or antagonistic activity. However, the structures of these imidazole derivatives are quite different from that of the present compounds. Thus, none of the imidazole derivatives disclosed in these publications have a ring structure fused to the imidazole group such as is the case in the present compounds.

In view of the arts interest in histamine H3 receptor agonists and antagonists, novel compounds which trigger the histamine H3 receptor would be a highly desirable contribution to the art. The present invention provides such a contribution to the art being based on the finding that a specific class of substituted imidazole compounds have a high and specific affinity to the histamine H3 receptor and possess histamine H3 receptor antagonistic activity. Some of these substituted imidazole derivatives are novel per se thereby constituting a further aspect of the invention.

Due to their histamine H3 receptor antagonistic activity the present compounds are useful in the treatment and/or prevention of a wide range of conditions and disorders in which a blockade of the histamine H3 receptor is beneficial. Thus, the compounds may find use e.g. in the treatment of diseases of the central nervous system, the peripheral nervous system, the cardiovascular system, the pulmonary system, the gastrointestinal system and the endocrinological system.

DEFINITIONS

In the structural formulas given herein and throughout the present specification, the following terms have the indicated meaning:

The term "C_{1-6}-alkyl" as used herein represent a branched or straight hydrocarbon group having from 1 to 6 carbon atoms. Typical C_{1-6}-alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, isopentyl, hexyl, isohexyl and the like.

The term "C_{2-8}-alkenyl" as used herein r presents a branched or straight hydrocarbon group having from 2 to 8 carbon atoms and at least one double bond. Examples of such groups include, but are not limited to, vinyl, 1-propenyl, 2-propenyl, allyl, iso-propenyl, 1,3-butadienyl, 1-butenyl, 2-butenyl, 1-pentenyl, 2-pentenyl, 1-hexenyl, 2-hexenyl, 1-heptenyl, 2-heptenyl, 1-octenyl, 2-octenyl and the like.

The term "C_{2-8}-alkynyl" as used herein represents a branched or straight hydrocarbon group having from 2 to 8 carbon atoms and at least one triple bond. Examples of such groups include, but are not limited to, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, 2-pentynyl, 1-hexynyl, 2-hexynyl, 1-heptynyl, 2-heptynyl, 1-octynyl, 2-octynyl and the like.

The term "C_{1-6}-alkoxy" as used herein, alone or in combination, refers to the radical -O-C_{1-6}-alkyl where C_{1-6}-alkyl is as defined above. Representative examples are methoxy, ethoxy, n-propoxy, isopropoxy, butoxy, *sec*-butoxy, *tert*-butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy and the like.

The term "C_{1-6}-alkylthio" as used herein, alone or in combination, refers to the radical -S-C_{1-6}-alkyl where C_{1-6}-alkyl is as defined above. Representative examples are methylthio, ethylthio, isopropylthio, propylthio, butylthio, pentylthio and the like.

The term "C_{3-15}-cycloalkyl" as used herein represents a carbocyclic group having from 3 to 15 carbon atoms such as from 3 to 8 carbon atoms. Representative examples are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl and the like.

The term "aryl" as used herein is intended to include carbocyclic aromatic ring systems such as phenyl, naphthyl (1-naphthyl or 2-naphthyl), anthracenyl (1-anthracenyl, 2-anthracenyl, 3-anthracenyl), phenanthrenyl, fluorenyl, indenyl and the like. Aryl is also intended to include the partially hydrogenated derivatives of the carbocyclic

systems enumerated above. Non-limiting examples of such partially hydrogenated derivatives are 1-(1,2,3,4-tetrahydronaphthyl) and 2-(1,2,3,4-tetrahydronaphthyl).

The term "aroyl" as used herein refers to the radical -CO-aryl where aryl is as defined above. Non-limiting examples are benzoyl, naphthoyl, anthracenoyl, phenanthrenoyl, fluorenoyl, indenoyl and the like.

The term "aryloxy" as used herein refers to the radical -O-aryl where aryl is as defined above. Non-limiting examples are phenoxy, naphthoxy, anthracenyloxy, phenantrenyloxy, fluorenyloxy, indenyloxy and the like.

The term "arylthio" as used herein refers to the radical -S-aryl where aryl is as defined above. Non-limiting examples are phenylthio, naphthylthio, phenanthrenylthio, fluorenylthio, indenylthio and the like.

The term "arylamino" as used herein refers to the radical -NH-aryl where aryl is as defined above. Non-limiting examples are phenylamino, naphthylamino, phenanthrenylamino, fluorenylamino, indenylamino and the like.

The term "arylsulfonyl" as used herein refers to the radical -$S(=O)_2$-aryl where aryl is as defined above. Non-limiting examples are phenylsulfonyl, naphthylsulfonyl, phenanthrenylsulfonyl, fluorenylsulfonyl, indenylsulfonyl and the like.

The term "heteroaryl" as used herein is intended to include heterocyclic aromatic ring systems containing one or more heteroatoms selected from nitrogen, oxygen and sulfur such as furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, tetrazolyl, thiadiazinyl, indolyl,

isoindolyl, benzofuryl, benzothienyl, benzothiophenyl (thianaphthenyl), indazolyl, benzimidazolyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, purinyl, quinazolinyl, quinolizinyl, quinolinyl, isoquinolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, azepinyl, diazepinyl, acridinyl and the like. Heteroaryl is also intended to include the partially or fully hydrogenated derivatives of the heterocyclic systems enumerated above. Non-limiting examples of such partially or fully hydrogenated derivatives are pyrrolinyl, pyrazolinyl, indolinyl, pyrrolidinyl, piperidinyl, piperazinyl, azepinyl, diazepinyl, morpholinyl, thiomorpholinyl, oxazolidinyl, oxazolinyl, oxazepinyl, aziridinyl and tetrahydofuranyl.

The term "heteroaroyl" as used herein refers to the radical -CO-heteroaryl where heteroaryl is as defined above. Non-limiting examples are furoyl, thienylcarbonyl, pyridoyl, oxazolylcarbonyl, benzofurylcarbonyl, benzimidazolylcarbonyl, pyrrolinylcarbonyl, azepinylcarbonyl and the like.

The term "heteroaryloxy" as used herein refers to the radical -O-heteroaryl where heteroaryl is as defined above. Non-limiting examples are furyloxy, thienyloxy, pyridyloxy, oxazolyloxy, benzofuryloxy, benzimidazolyloxy, pyrrolinyloxy, azepinyloxy and the like.

The term "heteroarylamino" as used herein refers to the radical -NH-heteroaryl where heteroaryl is as defined above. Non-limiting examples are furylamino, thienylamino, pyridylamino, oxazolylamino, benzofurylamino, benzimidazolylamino, pyrrolinylamino, azepinylamino and the like.

The term "heteroarylthio" as used herein refers to the radical -S-heteroaryl where heteroaryl is as defined above. Non-limiting examples are furylthio, thienylthio, pyridylthio, oxazolylthio, benzofurylthio, benzimidazolylthio, pyrrolinylthio, azepinylthio and the like.

The term "heteroarylsulfonyl" as used herein refers to the radical -S(=O)$_2$-heteroaryl where heteroaryl is as defined above. Non-limiting examples are furylsulfonyl, thienylsulfonyl, pyridylsulfonyl, oxazolylsulfonyl, benzofurylsulfonyl, benzimidazolylsulfonyl, pyrrolinylsulfonyl, azepinylsulfonyl and the like.

The term "acylamino" as used herein represents a radical of the form -N(L)-C(=O)-G where G and L independently represent hydrogen, C_{1-6}-alkyl, aryl or heteroaryl as defined above. Non-limiting examples are acetylamino, propanoylamino, butyryl-amino, pentanoylamino, benzoylamino, furoylamino, pyridoylamino and the like.

The term "sulfonylamino" as used herein represents a radical of the form -N(L)-S(=O)$_2$-G where G and L independently represent hydrogen, C_{1-6}-alkyl, aryl or heteroaryl as defined above. Non-limiting examples are methanesulfonylamino, propanesulfonylamino, benzenesulfonylamino, N-methyl-N-(benzenesulfonyl)amino, 4-methylbenzenesulfonylamino N-butyl-N-(4-methylbenzenesulfonyl)amino, 2-thienylsulfonylamino and the like.

The term "halogen" means fluorine, chlorine, bromine or iodine.

As used herein, the phrase "3 to 8 membered, saturated or unsaturated, carbocyclic or heterocyclic ring" is intended to include carbocyclic rings which are saturated or contain one or more double bonds as well as heterocyclic rings containing one or more heteroatoms selected from nitrogen, oxygen or sulfur which are saturated or contain one or more double bonds.

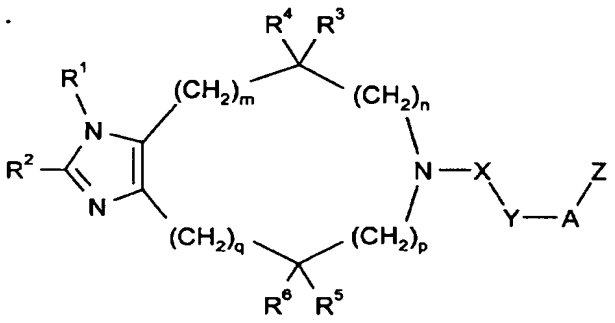
The term "optionally substituted" as used herein means that the groups in question are either unsubstituted or substituted with one or more of the substituents specified. When the groups in question are substituted with more than one substituent the substituents may be the same or different.

As used herein, the phrase "a functional group which can be converted to hydrogen *in vivo*" is intended to include any group which upon administering the present compounds to the subjects in need thereof can be converted to hydrogen e.g. enzymatically or by the acidic environment in the stomach. Non-limiting examples of such groups are acyl, carbamoyl, monoalkylated carbamoyl, dialkylated carbamoyl, alkoxycarbonyl, alkoxyalkyl groups and the like such as C_{1-6}-alkanoyl, aroyl, C_{1-6}-alkylcarbamoyl, di-C_{1-6}-alkylcarbamoyl, C_{1-6}-alkoxycarbonyl and C_{1-6}-alkoxy-C_{1-6}-alkyl.

Certain of the above defined terms may occur more than once in the structural formulas, and upon such occurrence each term shall be defined independently of the other.

DESCRIPTION OF THE INVENTION

The present invention relates to novel, substituted imidazoles of the general formula I



I

wherein

R^1 is hydrogen or a functional group which can be converted to hydrogen *in vivo*;

R^2 is hydrogen, C_{1-6}-alkyl, halogen, cyano, trifluoromethyl, hydroxy or -NR^7R^8

wherein R^7 and R^8 independently are

hydrogen;

C_{1-6}-alkyl optionally substituted with aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroarylamino or C_{3-8}-cycloalkyl which are optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

aryl optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

heteroaryl optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

aroyl optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

heteroaroyl optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

arylsulfonyl optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

heteroarylsulfonyl optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino; or

C_{1-6}-alkylsulfonyl optionally substituted with C_{3-8}-cycloalkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino; or

R^7 and R^8, together with the nitrogen atom to which they are connected, form a 3 to 8 membered, saturated or unsaturated, carbocyclic or heterocyclic ring optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

R^3, R^4, R^5 and R^6 independently are

hydrogen; carboxy; C_{1-6}-alkoxycarbonyl; -CO-NR^7R^8 wherein R^7 and R^8 are as defined above; cyano; or halogen;

C_{3-8}-cycloalkyl optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

C_{1-6}-alkyl optionally substituted with

C_{1-6}-alkoxy; C_{1-6}-alkylthio; hydroxy; cyano; halogen; trifluoromethyl; carboxy; C_{1-6}-alkoxycarbonyl; or -CO-NR^7R^8 wherein R^7 and R^8 are as defined above; or C_{3-8}-cycloalkyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino which are optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

C_{2-6}-alkenyl optionally substituted with

C_{1-6}-alkoxy; C_{1-6}-alkylthio; hydroxy; cyano; halogen; trifluoromethyl; carboxy; C_{1-6}-alkoxycarbonyl; or -CO-NR^7R^8 wherein R^7 and R^8 are as defined above; or C_{3-8}-cycloalkyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino which are optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

C_{2-6}-alkynyl optionally substituted with

C_{1-6}-alkoxy; C_{1-6}-alkylthio; hydroxy; cyano; halogen; trifluoromethyl; carboxy; C_{1-6}-alkoxycarbonyl; or -CO-NR^7R^8 wherein R^7 and R^8 are as defined above; or C_{3-8}-cycloalkyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino which are optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino; or

aryl optionally substituted with halogen, cyano, nitro, C_{1-6}-alkyl, C_{1-6}-alkoxy, hydroxy, trifluoromethyl, aryl, heteroaryl, aryloxy, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroarylamino or -CO-NR^7R^8 wherein R^7 and R^8 are as defined above ; or

R^3 and R^4, together with the carbon atom to which they are connected, and/or R^5 and R^6 together with the carbon atom to which they are connected, form a 3 to 8 membered, saturated or unsaturated, carbocyclic or heterocyclic ring optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

m, n, p and q independently are 0, 1 or 2;

X is a valence bond, $-CH_2-$, -C(=O)-, -C(=S)-, -S(=O)-, $-S(=O)_2-$, -C(=N-CN)-, $-C(=CH-NO_2)-$, $-C[=C(CN)_2]-$, -C(=CH-CN)-, or $-C(=NR^7)-$ wherein R^7 is as defined above;

Y is a valence bond, -O- or $-N(R^7)-$ wherein R^7 is as defined above;

A is a valence bond, C_{1-8}-alkylene, C_{2-8}-alkenylene, C_{2-8}-alkynylene, C_{3-8}-cycloalkylene or phenylene; or

when Y is $-N(R^7)-$, A may together with R^7 form a 3 to 8 membered, saturated or unsaturated, carbocyclic or heterocyclic ring optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino; and

Z is $-R^9$, $-OR^9$, $-SR^9$, $-NR^9R^{10}$, $-CHR^9R^{10}$ or $=CR^9R^{10}$

wherein R^9 and R^{10} independently are

hydrogen;

C_{1-6}-alkyl optionally substituted with aryl, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, heteroaryl or C_{3-8}-cycloalkyl which are optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, hydroxy, amino, halogen, cyano or trifluoromethyl;

C_{2-6}-alkenyl optionally substituted with aryl, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy,

acylamino, heteroaryl or C_{3-8}-cycloalkyl which are optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, hydroxy, amino, halogen, cyano or trifluoromethyl;

C_{2-6}-alkynyl optionally substituted with aryl, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, heteroaryl or C_{3-8}-cycloalkyl which are optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, hydroxy, amino, halogen, cyano or trifluoromethyl;

aryl optionally substituted with aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano or trifluoromethyl;

C_{3-15}-cycloalkyl optionally substituted with aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano or trifluoromethyl;

aroyl optionally substituted with aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino,

C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano or trifluoromethyl; or

heteroaryl optionally substituted with aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano or trifluoromethyl; or

R^9 and R^{10} are joined by one or more bridging linkers such as a valence bond, C_{1-4}-alkylene, C_{2-4}-alkenylene, -O-, -S-, -N(R^7)-, -C(=O)-, -S(=O)-, -S(=O)$_2$-, -C(R^7R^8)-, phenylene, biphenylene, -O-C_{1-4}-alkylene, -S-C_{1-4}-alkylene, -N(R^7)-C_{1-4}-alkylene, -N=C_{1-4}-alkylene, -O-C_{2-4}-alkenylene, -S-C_{2-4}-alkenylene, or -N(R^7)-C_{2-4}-alkenylene, to form a mono-, bi- or polycyclic ring system; or

when Y is -N(R^7)-, R^9 or R^{10} may together with R^7 form a 3 to 8 membered, saturated or unsaturated, carbocyclic or heterocyclic ring optionally substituted with aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano or trifluoromethyl;

with the provisos that

when X is -CS-, R^1 = R^2 = R^5 = R^6 = hydrogen, m = n = p = 0 and q = 1, the group -Y-A-Z must not start with the radical -NH-;

when the group -X-Y-A-Z starts with the radical -CH_2-, R^1 = R^2 = R^6 = hydrogen, m = n = p = 0 and q = 1, R^5 must not be carboxy or aminocarbonyl;

when X is -CO-, the group -Y-A-Z starts with the radical -NH-, $R^1 = R^2 = R^6$ = hydrogen, m = n = p = 0 and q = 1, the remainder of the group -Y-A-Z must not be hydrogen, unsubstituted or C_{1-6}-alkoxy substituted phenyl, unsubstituted C_{3-8}-cycloalkyl or unsubstituted C_{1-6}-alkyl;

when X is -CO-, the group -Y-A-Z starts with the radical -O-, $R^1 = R^2 = R^6$ = hydrogen, m = n = p = 0 and q = 1, R^5 must not be carboxy, aminocarbonyl or hydrogen;

when -X is -CO-, the group -Y-A-Z starts with the radical -CH<, $R^1 = R^2 = R^3 = R^4 = R^6$ = hydrogen, m = n = p = 0 and q = 1, R^5 must not be hydroxymethyl, C_{1-6}-alkoxycarbonyl or carboxy; and

when X is -CO-, the group -Y-A-Z is 4-methoxyphenyl, $R^1 = R^2 = R^3 = R^4 = R^6$ = hydrogen, m = n = p = 0 and q = 1, R^5 must not be carboxy;

and a pharmaceutically acceptable salt thereof or any optical isomer thereof or mixture of optical isomers, including a racemic mixture, or any tautomeric form.

In a preferred embodiment of the invention m, n, and p are 0 and q is 1.

In another preferred embodiment of the invention R^1 and R^2 are both hydrogen.

In still another preferred embodiment of the invention R^5 and R^6 are both hydrogen.

A further preferred embodiment of the invention are the compounds of the formula I as defined above wherein X is -C(=O)-; Y is a valence bond; A is a valence bond or C_{1-8}-alkylene; and Z is $-R^9$ or $-CHR^9R^{10}$; as well as pharmaceutically acceptable salts thereof or any optical isomers thereof or mixtures of optical isomers, including a racemic mixture, or any tautomeric forms.

A further preferred embodiment of the invention are the compounds of the formula I as defined above wherein X is -C(=O)-; Y is a valence bond; A is a valence bond or C_{1-8}-alkylene; Z is $-R^9$ or $-CHR^9R^{10}$; $R^1 = R^2$ = hydrogen; and m = n = p = 0 and q = 1; as well as pharmaceutically acceptable salts thereof or any optical isomers thereof or mixtures of optical isomers, including a racemic mixture, or any tautomeric forms.

A particularly preferred group of the compounds of the formula I as defined above are such compounds wherein X is -C(=O)-; Y is a valence bond; A is a valence bond or C_{1-8}-alkylene; $R^1 = R^2$ = hydrogen; m = n = p = 0 and q = 1; and Z is $-R^9$ in which R^9 is

aryl, C_{3-15}-cycloalkyl, aroyl or heteroaryl which are optionally substituted with aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano or trifluoromethyl;

as well as pharmaceutically acceptable salts thereof or any optical isomers thereof or mixtures of optical isomers, including a racemic mixture, or any tautomeric forms.

A further particularly preferred group of the compounds of the formula I as defined above are such compounds wherein X is -C(=O)-; Y is a valence bond; A is a valence bond or C_{1-8}-alkylene; $R^1 = R^2$ = hydrogen; m = n = p = 0 and q = 1; and Z is $-CHR^9R^{10}$ in which R^9 and R^{10} independently are

hydrogen; or

aryl, C_{3-15}-cycloalkyl, aroyl or heteroaryl which are optionally substituted with aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino,

aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano or trifluoromethyl;

as well as pharmaceutically acceptable salts thereof or any optical isomers thereof or mixtures of optical isomers, including a racemic mixture, or any tautomeric forms.

When R^9 and/or R^{10} represent aryl, aroyl or C_{3-15}-cycloalkyl they are preferably phenyl, benzoyl or C_{3-8}-cycloalkyl, such as cyclohexyl, respectively.

Another preferred embodiment of the invention are the compounds of the formula I as defined above wherein $R^1 = R^2$ = hydrogen; m = n = p = 0 and q = 1; X is C(=O)-; Y is a valence bond; A is a valence bond or C_{1-8}-alkylene; and Z is $-NR^9R^{10}$ or $-CHR^9R^{10}$ in which R^9 and R^{10} independently represent

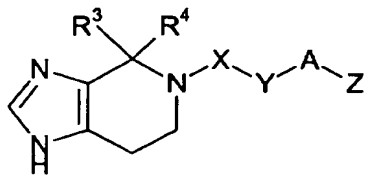
hydrogen; or

aryl, C_{3-15}-cycloalkyl, aroyl or heteroaryl which are optionally substituted with aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano or trifluoromethyl;

which are joined with a C_{1-4}-alkylene group to form a cyclic ring system;

as well as pharmaceutically acceptable salts thereof or any optical isomers thereof or mixtures of optical isomers, including a racemic mixture, or any tautomeric forms.

Specific examples of the above preferred embodiments of the present invention are the following compounds of the formula



wherein

Ex. No.	R^3	R^4	X	Y	A	Z
14-002	H	H	CO	bond	bond	cyclohexylmethyl
14-004	H	H	CO	bond	bond	3-(4-fluorophenyl)-3-oxopropyl
14-003	H	H	CO	bond	bond	cyclohexyl
14-005	H	H	CO	bond	bond	6-phenyl-6-oxohexyl
4	H	H	CO	bond	bond	2-cyclohexylethyl
3	H	H	CO	bond	bond	5-phenylpentyl
2	H	H	CO	bond	bond	4-cyclohexylbutyl
	H	H	CO	bond	bond	methyl
6	H	H	CO	bond	bond	2,2-diphenylethyl
8	H	H	CO	bond	bond	2-(10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)ethyl
1	CH_3	CH_3	CO	bond	bond	2-cyclohexylethyl
5	H	4-isopropylphenyl	CO	bond	bond	2-(4-fluorophenyl)ethyl
7	CH_3	CH_2CH_3	CO	bond	bond	2-cyclohexylethyl
9	spiro-	$-(CH_2)_3-$	CO	bond	bond	2-cyclohexylethyl

Another preferred embodiment of the invention are the compounds of the formula I as defined above wherein $R^1 = R^2$ = hydrogen; m = n = p = 0 and q = 1; X is -C(=O)-; Y is -NH-; A is a valence bond, C_{1-8}-alkylene or C_{3-8}-cycloalkylene; and

Z is -R^9 in which R^9 is

C_{1-6}-alkyl optionally substituted with aryl, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, heteroaryl or C_{3-8}-cycloalkyl which are optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, hydroxy, amino, halogen, cyano or trifluoromethyl;

aryl optionally substituted with aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano or trifluoromethyl;

C_{3-15}-cycloalkyl optionally substituted with aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano or trifluoromethyl; or

heteroaryl optionally substituted with aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano or trifluoromethyl; or

Z is -CHR^9R^{10} in which R^9 and R^{10} independently are

hydrogen;

C_{1-6}-alkyl optionally substituted with aryl, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, heteroaryl or C_{3-8}-cycloalkyl which are optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, aryl-C_{1-6}- alkyl, heteroaryl-C_{1-6}-alkyl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, hydroxy, amino, halogen, cyano or trifluoromethyl;

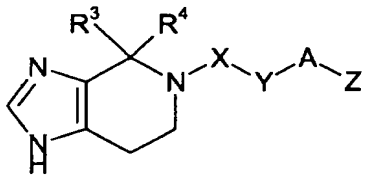
aryl optionally substituted with aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano or trifluoromethyl;

C_{3-15}-cycloalkyl optionally substituted with aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano or trifluoromethyl; or

heteroaryl optionally substituted with aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano or trifluoromethyl;

as well as pharmaceutically acceptable salts thereof or any optical isomers thereof or mixtures of optical isomers, including a racemic mixture, or any tautomeric forms.

Specific examples of such compounds are the following compounds of the formula



wherein

Ex. No.	R^3	R^4	X	Y	A	Z
10-001	H	H	CO	NH	$-(CH_2)_2-$	2-thienyl
10-002	H	H	CO	NH	bond	3,5-dimethyl-1,2-oxazol-4-yl
10-003	H	H	CO	NH	$-CH(CH_3)-$	1-naphthyl
10-004	H	H	CO	NH	bond	2-phenylcyclopropyl
10-005	H	H	CO	NH	bond	1-(4-bromophenyl)ethyl
10-006	H	H	CO	NH	bond	2-(trifluoromethyl)phenyl
10-007	H	H	CO	NH	bond	2-phenylethyl
10-008	H	H	CO	NH	bond	4-(trifluoromethyl)phenyl
10-009	H	H	CO	NH	bond	3-cyanophenyl
10-010	H	H	CO	NH	bond	4-cyanophenyl
10-011	H	H	CO	NH	bond	n-octyl
11	H	H	CO	NH	bond	(2,4-dichlorophenyl)methyl
12	H	2-cyclohexylethyl	CO	NH	bond	ethyl
13	H	2-cyclohexylethyl	CO	NH	bond	(2,4-dichlorophenyl)methyl

R^3 and R^4 which may be the same or different are preferably selected from the group consisting of

hydrogen;

C_{3-8}-cycloalkyl optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

C_{1-6}-alkyl optionally substituted by C_{3-8}-cycloalkyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino which are optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino; or

aryl optionally substituted with halogen, cyano, nitro, C_{1-6}-alkyl, C_{1-6}-alkoxy, hydroxy, trifluoromethyl, aryl, heteroaryl, aryloxy, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroarylamino or -CO-NR^7R^8 wherein R^7 and R^8 are as defined above ; or

R^3 and R^4, together with the carbon atom to which they are connected, and/or R^5 and R^6 together with the carbon atom to which they are connected, form a C_{3-8}-cycloalkyl ring optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino.

More preferred, one of R^3 and R^4 represents hydrogen while the other has the meaning stated above such as C_{3-8}-cycloalkyl substituted C_{1-6}-alkyl; C_{3-8}-cycloalkyl or aryl such as phenyl which are optionally substituted as defined above; or R^3 and R^4 both represent unsubstituted C_{1-6}-alkyl such as methyl or ethyl; or R^3 and R^4 together with the carbon atom to which they are connected form a C_{3-8}-cycloalkyl group such as spirocyclobutane or spirocyclopentane optionally substituted as defined above.

In another preferred embodiment of the invention m, n and p are 0, q is 1 and R^3 and R^4 are both hydrogen or are both C_{1-6}-alkyl optionally substituted as defined above for formula I or R^3 and R^4, together with the carbon atom to which they are connec-

ted, form a C_{3-8}-cycloalkyl ring optionally substituted as defined above for formula I. Preferably, the C_{1-6}-alkyl groups and the C_{3-8}-cycloalkyl ring are unsubstituted.

In a further preferred embodiment of the invention R^3, R^4, R^5 and R^6 are hydrogen.

The compounds of the present invention may have one or more asymmetric centres and it is intended that any optical isomers, as separated, pure or partially purified optical isomers or racemic mixtures thereof are included in the scope of the invention.

The present invention also encompasses pharmaceutically acceptable salts of the present compounds. Such salts include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts, ammonium and alkylated ammonium salts. Acid addition salts include salts of inorganic acids as well as organic acids. Representative examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric acids and the like. Representative examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, lactic, maleic, malic, malonic, mandelic, oxalic, picric, pyruvic, salicylic, succinic, methanesulfonic, ethanesulfonic, tartaric acids and the like. Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in *J. Pharm. Sci.* **1977**, *66*, 2, which is incorporated herein by reference. Examples of metal salts include lithium, sodium, potassium, magnesium salts and the like. Examples of ammonium and alkylated ammonium salts include ammonium, methylammonium, dimethylammonium, trimethylammonium, ethylammonium, hydroxyethylammonium, diethylammonium, butylammonium, tetramethylammonium salts and the like.

Also intended as pharmaceutically acceptable acid addition salts are the hydrates which the present compounds are able to form.

The acid addition salts may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid, and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent.

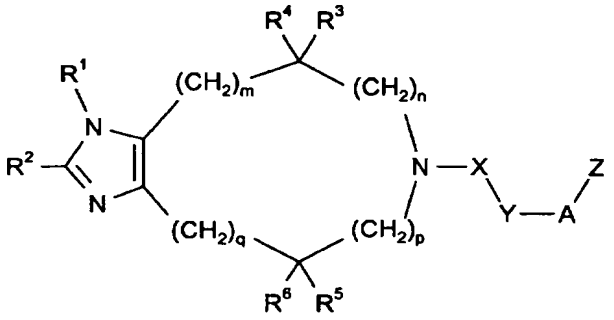
The compounds of the present invention may form solvates with standard low molecular weight solvents using methods known to the skilled artisan. Such solvates are also contemplated as being within the scope of the present invention.

The compounds of the present invention interact with the histamine H3 receptor and may thus be used for the treatment of a wide range of disorders related to the histamine H3 receptor.

Accordingly, in another aspect the present invention relates to a compound of the general formula I or a pharmaceutically acceptable salt thereof or any optical isomer thereof or mixture of optical isomers, including a racemic mixture, or any tautomeric form for use as a medicament.

The invention also relates to pharmaceutical compositions comprising, as an active ingredient, at least one compound of the formula I or a pharmaceutically acceptable salt thereof or any optical isomer thereof or mixture of optical isomers, including a racemic mixture, or any tautomeric form together with one or more pharmaceutically acceptable carriers or diluents.

Furthermore, the invention relates to the use of a compound of the general formula I'



I'

wherein

R^1 is hydrogen or a functional group which can be converted to hydrogen *in vivo*;

R^2 is hydrogen, C_{1-6}-alkyl, halogen, cyano, trifluoromethyl, hydroxy or $-NR^7R^8$

wherein R^7 and R^8 independently are

hydrogen;

C_{1-6}-alkyl optionally substituted with aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroarylamino or C_{3-8}-cycloalkyl which are optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

aryl optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

heteroaryl optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

aroyl optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

heteroaroyl optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

arylsulfonyl optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

heteroarylsulfonyl optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino; or

C_{1-6}-alkylsulfonyl optionally substituted with C_{3-8}-cycloalkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino; or

R^7 and R^8, together with the nitrogen atom to which they are connected, form a 3 to 8 membered, saturated or unsaturated, carbocyclic or heterocyclic ring optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

R^3, R^4, R^5 and R^6 independently are

hydrogen; carboxy; C_{1-6}-alkoxycarbonyl; -CO-NR^7R^8 wherein R^7 and R^8 are as defined above; cyano; or halogen;

C_{3-8}-cycloalkyl optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

C_{1-6}-alkyl optionally substituted with

C_{1-6}-alkoxy; C_{1-6}-alkylthio; hydroxy; cyano; halogen; trifluoromethyl; carboxy; C_{1-6}-alkoxycarbonyl; or -CO-NR^7R^8 wherein R^7 and R^8 are as defined above; or C_{3-8}-cycloalkyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino which are optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

C_{2-6}-alkenyl optionally substituted with

C_{1-6}-alkoxy; C_{1-6}-alkylthio; hydroxy; cyano; halogen; trifluoromethyl; carboxy; C_{1-6}-alkoxycarbonyl; or -CO-NR^7R^8 wherein R^7 and R^8 are as defined above; or C_{3-8}-cycloalkyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino which are optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

C_{2-6}-alkynyl optionally substituted with

C_{1-6}-alkoxy; C_{1-6}-alkylthio; hydroxy; cyano; halogen; trifluoromethyl; carboxy; C_{1-6}-alkoxycarbonyl; or -CO-NR^7R^8 wherein R^7 and R^8 are as defined above; or C_{3-8}-cycloalkyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino which are optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino; or

aryl optionally substituted with halogen, cyano, nitro, C_{1-6}-alkyl, C_{1-6}-alkoxy, hydroxy, trifluoromethyl, aryl, heteroaryl, aryloxy, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroarylamino or -CO-NR^7R^8 wherein R^7 and R^8 are as defined above ; or

R^3 and R^4, together with the carbon atom to which they are connected, and/or R^5 and R^6 together with the carbon atom to which they are connected, form a 3 to 8 membered, saturated or unsaturated, carbocyclic or heterocyclic ring optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

m, n, p and q independently are 0, 1 or 2;

X is a valence bond, -CH_2-, -C(=O)-, -C(=S)-, -S(=O)-, -$S(=O)_2$-, -C(=N-CN)-, -C(=CH-NO_2)-, -C[=$C(CN)_2$]-, -C(=CH-CN)-, or -C(=NR^7)- wherein R^7 is as defined above;

Y is a valence bond, -O- or -N(R^7)- wherein R^7 is as defined above;

A is a valence bond, C_{1-8}-alkylene, C_{2-8}-alkenylene, C_{2-8}-alkynylene, C_{3-8}-cycloalkylene or phenylene; or

when Y is -N(R^7)-, A may together with R^7 form a 3 to 8 membered, saturated or unsaturated, carbocyclic or heterocyclic ring optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino; and

Z is -R^9, -OR^9, -SR^9, -NR^9R^{10}, -CHR^9R^{10} or =CR^9R^{10}

wherein R^9 and R^{10} independently are

hydrogen;

C_{1-6}-alkyl optionally substituted with aryl, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, heteroaryl or C_{3-8}-cycloalkyl which are optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, hydroxy, amino, halogen, cyano or trifluoromethyl;

C_{2-6}-alkenyl optionally substituted with aryl, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, heteroaryl or C_{3-8}-cycloalkyl which are optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, hydroxy, amino, halogen, cyano or trifluoromethyl;

C_{2-6}-alkynyl optionally substituted with aryl, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, heteroaryl or C_{3-8}-cycloalkyl which are optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, hydroxy, amino, halogen, cyano or trifluoromethyl;

aryl optionally substituted with aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino,

C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano or trifluoromethyl;

C_{3-15}-cycloalkyl optionally substituted with aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano or trifluoromethyl;

aroyl optionally substituted with aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano or trifluoromethyl; or

heteroaryl optionally substituted with aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano or trifluoromethyl; or

R^9 and R^{10} are joined by one or more bridging linkers such as a valence bond, C_{1-4}-alkylene, C_{2-4}-alkenylene, -O-, -S-, -N(R^7)-, -C(=O)-, -S(=O)-, -S(=O)$_2$-, -C(R^7R^8)-, phenylene, biphenylene, -O-C_{1-4}-alkylene, -S-C_{1-4}-alkylene, -N(R^7)-C_{1-4}-alkylene, -N=C_{1-4}-alkylene, -O-C_{2-4}-alkenylene, -S-C_{2-4}-alkenylene, or -N(R^7)-C_{2-4}-alkenylene, to form a mono-, bi- or polycyclic ring system; or

when Y is -N(R^7)-, R^9 or R^{10} may together with R^7 form a 3 to 8 membered, saturated or unsaturated, carbocyclic or heterocyclic ring optionally substituted with aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino,

aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano or trifluoromethyl;

or a pharmaceutically acceptable salt thereof or any optical isomer thereof or mixture of optical isomers, including a racemic mixture, or any tautomeric form for the preparation of a medicament for the treatment of disorders related to the histamine H3 receptor.

In still another aspect, the invention relates to a method for the treatment of disorders related to the histamine H3 receptor the method comprising administering to a subject in need thereof an effective amount of a compound of the formula I' or a pharmaceutically acceptable salt thereof or any optical isomer thereof or mixture of optical isomers, including a racemic mixture, or any tautomeric form or a pharmaceutical composition comprising the same.

More particularly, the present compounds possess histamine H3 receptor antagonistic activity and are accordingly useful in the treatment of a wide range of conditions and disorders in which a histamine H3 receptor blockade is beneficial.

The compounds of the present invention may thus be used for the treatment of airway disorders such as asthma, as anti-diarrhoeals and for the modulation of gastric acid secretion.

The compounds of the present invention may also be used for the treatment of diseases associated with the regulation of sleep and wakefulness and for the treatment of narcolepsy and attention deficite disorders.

Moreover, the compounds of the invention may be used as stimulants or as sedatives.

The compounds of the invention may also be useful for the treatment of eating disorders such as anorexia or bulimia by virtue of their appetite regulating properties.

Furthermore, the present compounds may be useful for the treatment and/or prevention of obesity as well as diseases related to obesity, such as diabetes and cardiovascular disorders.

The present compounds may also be used for the treatment of conditions associated with epilepsy. Additionally, the present compounds may be used for the treatment of motion sickness and vertigo, and useful as regulators of hypothalamo-hypophyseal secretion, antidepressants, modulators of cerebral circulation, and in the treatment of irritable bowel syndrome.

Further, the compounds of the present invention may be used for the treatment of dementia and Alzheimer's disease. Moreover, the compounds of the present invention may be used as analgetics and for the treatment of inflammatory painful conditions or neurogenic inflammation.

These new compounds may also interact with the vanilloid receptors, the serotonine receptors, and the adrenergic receptors and may be useful for the treatment of diseases associated with these receptors. Hence, the compounds of the present invention may be vanilloid receptor agonists, and thus be useful for the treatment of obesity by enhancement of the metabolic rate and energy expenditure. Further, by virtue of their interaction with the vanilloid receptor the compounds of the present invention may be useful for the treatment of pain or neurogenic inflammation or inflammatory painful conditions.

Furthermore, by virtue of their interaction with the 5-HT3 receptor (serotonine-3-receptor), the compounds of the present invention may be useful as antiemetics, in particular the chemotherapy-induced emesis. Further potential applications of 5-HT3

antagonists include treatment of central nervous system disorders such as anxiety, schizophrenia, drug abuse and withdrawal symptoms, and pathological and age-associated amnesia.

Furthermore, the present compounds may be alpha-2-adrenoceptor agonists or antagonists and thus be useful for the treatment of hypertension and of conditions associated with overexpression or hypersensitization of adrenergic alpha-2 receptors, especially obesity, withdrawal symptoms to an adrenergic alpha-2 agonist, neurological disorders (especially orthostatic hypotension), multiple system atrophy, diabetes mellitus, benign prostatic hyperplasia or drug induced sensitization of adrenergic alpha-2 receptors. Moreover, the compounds of the present invention, by virtue of their interaction with alpha-2 receptors, may be useful as sedatives and hypnotics (sleep inducing agents) or as stimulants.

In a preferred embodiment of the invention the present compounds are used for the treatment and/or prevention of eating disorders such as bulimia or anorexia or for the treatment and/or prevention of obesity and diseases related to obesity such as diabetes, including NIDDM (non-insulino dependent diabetes mellitus), and cardiovascular diseases.

PHARMACEUTICAL COMPOSITIONS

The compounds of the invention may be administered alone or in combination with pharma-ceutically acceptable carriers or excipients, in either single or multiple doses. The pharmaceutical compositions according to the invention may be formulated with pharmaceutically acceptable carriers or diluents as well as any other known adjuvants and excipients in accordance with conventional techniques such as those disclosed in Remington: The Science and Practice of Pharmacy,19th Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

The pharmaceutical compositions may be specifically formulated for administration by any suitable route such as the oral, rectal, nasal, pulmonary, topical (including buccal and sublingual), transdermal, intracisternal, intraperitoneal, vaginal and parenteral (including subcutaneous, intramuscular, intrathecal, intravenous and intradermal) route, the oral route being preferred. It will be appreciated that the preferred route will depend on the general condition and age of the subject to be treated, the nature of the condition to be treated and the active ingredient chosen.

Pharmaceutical compositions for oral administration include solid dosage forms such as capsules, tablets, dragees, pills, lozenges, powders and granules. Where appropriate, they can be prepared with coatings such as enteric coatings or they can be formulated so as to provide controlled release of the active ingredient such as sustained or prolonged release according to methods well-known in the art.

Liquid dosage forms for oral administration include solutions, emulsions, suspensions, syrups and elixirs.

Pharmaceutical compositions for parenteral administration include sterile aqueous and non-aqueous injectable solutions, dispersions, suspensions or emulsions as well as sterile powders to be reconstituted in sterile injectable solutions or dispersions prior to use. Depot injectable formulations are also contemplated as being within the scope of the present invention.

Other suitable administration forms include suppositories, sprays, ointments, cremes, gels, inhalants, dermal patches, implants etc.

A typical oral dosage is in the range of from about 0.001 to about 100 mg/kg body weight per day, preferably from about 0.01 to about 50 mg/kg body weight per day, and more preferred from about 0.05 to about 10 mg/kg body weight per day administered in one or more dosages such as 1 to 3 dosages. The exact dosage will de-

pend upon the frequency and mode of administration, the sex, age, weight and general condition of the subject treated, the nature and severity of the condition treated and any concomitant diseases to be treated and other factors evident to those skilled in the art.

The formulations may conveniently be presented in unit dosage form by methods known to those skilled in the art. A typical unit dosage form for oral administration one or more times per day such as 1 to 3 times per day may contain of from 0.05 to about 1000 mg, preferably from about 0.1 to about 500 mg, and more preferred from about 0.5 mg to about 200 mg.

For parenteral routes, such as intravenous, intrathecal, intramuscular and similar administration, typically doses are in the order of about half the dose employed for oral administration.

The compounds of this invention are generally utilized as the free substance or as a pharmaceutically acceptable salt thereof. One example is an acid addition salt of a compound having the utility of a free base. When a compound according to the invention contains a free base such salts are prepared in a conventional manner by treating a solution or suspension of a free base of the compound according to the invention with a chemical equivalent of a pharmaceutically acceptable acid, for example, inorganic and organic acids. Representative examples are mentioned above. Physiologically acceptable salts of a compound with a hydroxy group include the anion of said compound in combination with a suitable cation such as sodium or ammonium ion.

For parenteral administration, solutions of the present compounds in sterile aqueous solution, aqueous propylene glycol or sesame or peanut oil may be employed. Such aqueous solutions should be suitable buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. The aqueous solutions are particularly suitable for intravenous, intramuscular, subcutaneous and intraperitoneal admini-

stration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solution and various organic solvents. Examples of solid carriers are lactose, terra alba, sucrose, cyclodextrin, talc, gelatine, agar, pectin, acacia, magnesium stearate, stearic acid or lower alkyl ethers of cellulose. Examples of liquid carriers are syrup, peanut oil, olive oil, phospholipids, fatty acids, fatty acid amines, polyoxyethylene or water. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The pharmaceutical compositions formed by combining the compounds according to the invention and the pharmaceutically acceptable carriers are then readily administered in a variety of dosage forms suitable for the disclosed routes of administration. The formulations may conveniently be presented in unit dosage form by methods known in the art of pharmacy.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules or tablets, each containing a predetermined amount of the active ingredient, and which may include a suitable excipient. These formulations may be in the form of powder or granules, as a solution or suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion.

If a solid carrier is used for oral administration, the preparation may be tabletted, placed in a hard gelatine capsule in powder or pellet form or it can be in the form of a troche or lozenge. The amount of solid carrier will vary widely but will usually be from about 25 mg to about 1 g. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatine capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

A typical tablet which may be prepared by conventional tabletting techniques may contain:

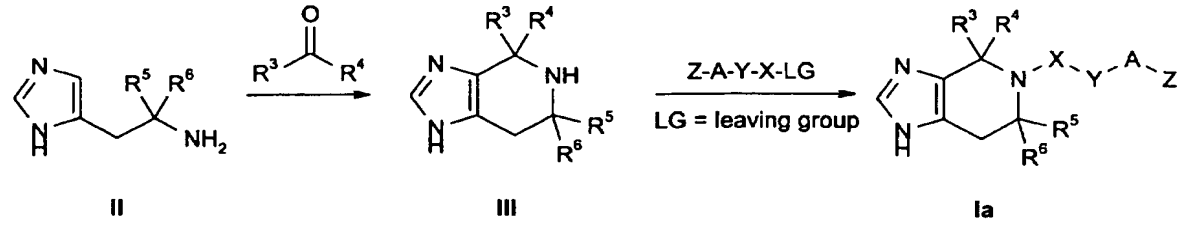
Core:	
Active compound (as free compound or salt thereof)	5.0 mg
Lactosum Ph. Eur.	67.8 mg
Cellulose, microcryst. (Avicel)	31.4 mg
Amberlite	1.0 mg
Magnesii stearas Ph. Eur.	q.s.
Coating:	
HPMC approx.	9 mg
Mywacett 9-40 T* approx.	0.9 mg

*Acylated monoglyceride used as plasticizer for film coating.

If desired, the pharmaceutical composition of the invention may comprise the compound of the formula I' in combination with further pharmacologically active substances.

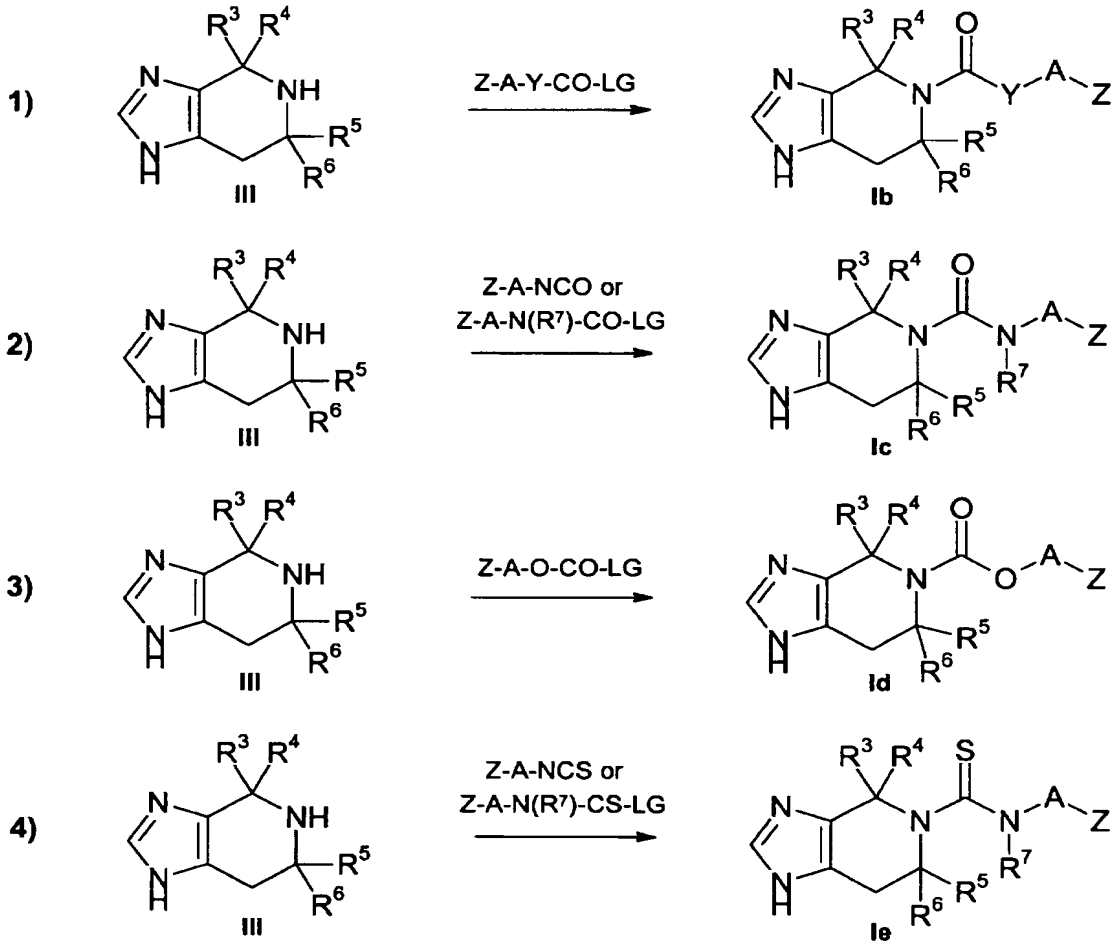
The preparation of the compounds of this invention can be realized in many different ways. The preparation of imidazoles of the formula **III** has been described in the literature (see e.g. F. B. Stocker et al., *J. Org.* Chem. **1966**, *31*, 2380; idem, ibid. **1990**, *55*, 3370; T. Vitali et al., *Il Farmaco* **1967**, *22*, 821; idem, ibid. **1965**, *20*, 634; S. Fränkel, K. Zeimer, *Biochemische Zeitschrift* **1920**, *110*, 238; G. Arcari et al., Fr. Pat. 1976, 2 337 726; DE 2700012, 1977, *Chem. Abstr., 87*, 201535).

Compounds of the formula **Ia**, wherein R^1 and R^2 are hydrogen, m = n = p = 0 and q = 1 can be prepared as outlined below:



II III Ia

More specifically, different types of compounds of the formula **Ia** of this invention can be prepared by the methods 1) to 4) sketched below:



III Ib Ic Id Ie

LG = leaving group

For instance, compounds of the formula **Ib** can be synthesized from 4,5,6,7-tetrahydroimidazo[4,5-c]pyridines III by treating the latter with suitable activated derivatives of carboxylic acids, such as acyl imidazoles, anhydrides, acid chlorides or active esters, or any of the derivatives commonly used for the preparation of carboxamides, under appropriate conditions.

Compounds of the formula **Ic** can be prepared by treating 4,5,6,7-tetrahydroimidazo[4,5-c]pyridines **III** with isocyanates Z-A-NCO or with synthetic equivalents thereof, such as carbamoyl chlorides Z-A-N(R^7)-CO-Cl under suitable conditions.

Compounds of the formula **Id** can be synthesized by treating 4,5,6,7-tetrahydroimidazo[4,5-c]pyridines **III** with haloformates Z-A-O-CO-Cl or with synthetic equivalents thereof such as activated carbonates (e.g. 4-nitrophenyl carbonates) under suitable conditions.

Finally, compounds of the formula **Ie** can be prepared by treating 4,5,6,7-tetrahydroimidazo[4,5-c]pyridines **III** with isothiocyanates Z-A-NCS or with synthetic equivalents thereof, such as thiocarbamoyl chlorides Z-A-N(R^7)-CS-Cl under suitable conditions.

The starting materials are either known compounds or compounds which may be prepared in analogy with the preparation of similar known compounds.

The present invention is further illustrated by the following representative examples, which are, however, not intended to limit the scope of the invention in any way.

EXAMPLES

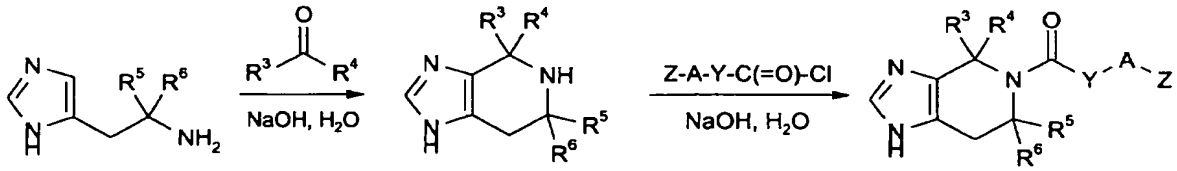
In the examples the following terms are intended to have the following, general meanings:

AcOH: glacial acetic acid
DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene
DCM: dichloromethane, methylenechloride
DIC: diisopropylcarbodiimide
DMF: N,N-dimethyl formamide
DMSO: dimethyl sulfoxide
EDC: N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride
FMoc: fluorenylmethyloxycarbonyl
HOBt: N-hydroxybenzotriazole, 1-hydroxybenzotriazole
NMP: N-methylpyrrolidone
TFA: trifluoroacetic acid
THF: tetrahydrofuran

NMR spectra were recorded on Bruker 300 MHz and 400 MHz instruments. HPLC-MS was performed on a Perkin Elmer instrument (API 100), and HPLC-systems from Merck-Hitachi (Hibar™ RT 250-4, Lichrosorb™ RP 18, 5.0 μm, 4.0 x 250 mm, gradient elution, 20% to 80% acetonitrile in water within 30 min, 1.0 mL/min, detection at 254 nm) and Waters (Symmetry™, C_{18}, 3.5 μm, 3.0 x 150 mm, gradient elution, 5% to 90% acetonitrile in water within 15 min, 1.0 mL/min, detection at 214 nm) were used.

Where stated the following general procedures were used:

General Procedure A:



II III Ib

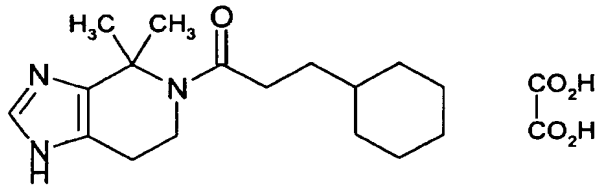
To a solution of the dihydrochloride of the amine **II** (10.0 mmol) in water (5 mL) an aqueous sodium hydroxide solution (12 N, 4.2 mL, 50.4 mmol), methanol (35 mL) and the carbonyl compound R^3R^4CO (25.0 mmol) were added. The resulting mixture was refluxed overnight, water (15 mL) was added, methanol was evaporated under reduced pressure and the residue was diluted with water to a volume of approximately 25 mL. The resulting mixture was washed with ether (2 x 50 mL, removal of excess ketone) and then, while stirring vigorously, the acyl halide (Z-A-Y-CO-Cl, 11.5 mmol) was added portionwise. After stirring for 10 min the mixture was extracted with DCM (2 x 100 mL). The combined organic phases were washed with water (25 mL), dried ($MgSO_4$) and concentrated. The remaining oil was redissolved in ethyl acetate (100 mL) and a solution of oxalic acid (0.45 g, 5.0 mmol) in ethyl acetate (25 mL) was added. After stirring for 30 min the precipitate was filtered off and dried under reduced pressure. Alternatively, the crude product **Ib** could be purified by column chromatography (silica gel, gradient elution with heptane/ethyl acetate/methanol).

General Procedure B:

A mixture of the dihydrochloride of the amine **II** (95 mmol), water (200 mL), and the carbonyl compound R^3R^4CO (133 mmol) was refluxed until no more amine **II** could be detected (HPLC). The mixture was then concentrated to dryness and the crude product **III** was purified by recrystallization.

The purified amine **III** was then acylated as in General Procedure A or by any other, conventional method.

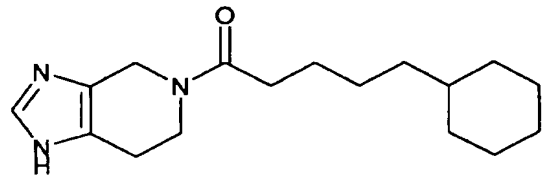
Example 1: 5-(3-Cyclohexylpropanoyl)-4,4-dimethyl-4,5,6,7-tetrahydroimidazo-[4,5-c]pyridine oxalic acid salt



Following the General Procedure A using histamine dihydrochloride (1.84 g, 10.0 mmol), acetone (4.0 mL) and 3-cyclohexylpropanoyl chloride (2.0 g, 11.5 mmol) 0.80 g (21%) of the title amide was obtained as oxalic acid salt.

HPLC (214 nm): elution at 18.59 min. LC-MS: Calcd. for MH^+: 290; found: 290. ^1H NMR (400 MHz, DMSO-d_6, two rotamers, 6:4): δ0.80-0.95 (m, 2H), 1.05-1.28 (m, 4H), 1.35-1.76 (m, 13H), 2.38 (m, 1.2H), 2.64 (t, J = 5 Hz, 1.2H), 2.89 (t, J = 5 Hz, 0.8H), 3.01 (t, J = 7 Hz, 0.8H), 3.54 (t, J = 5 Hz, 0.8H), 3.58 (t, J = 5 Hz, 1.2H), 8.25 (s, 0.6H), 8.34 (s, 0.4H).

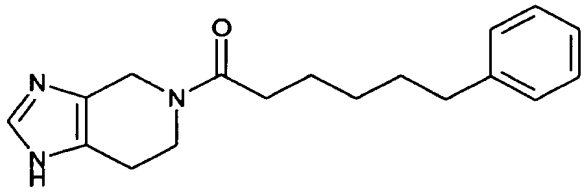
Example 2: 5-(5-Cyclohexylpentanoyl)-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine



To a solution of 5-cyclohexylpentanoic acid (0.94 g, 5.10 mmol) in DCM (4 mL) carbonyldiimidazole (0.83 g, 5.12 mmol) was added. The resulting mixture was stirred at room temperature for 16 h and then added to a solution of 4,5,6,7-tetrahydroimidazo[4,5-c]pyridine (5.10 mmol) in DCM (4 mL). After 2.5 h DCM (50 mL) was added and the mixture was washed with water (3 x 15 mL). The organic layer was then dried ($MgSO_4$) and concentrated. The crude product was purified by column chromatography (silica gel, ethyl acetate/methanol 9:1) whereby 0.35 g (24%) of the title amide was obtained as an oil.

HPLC (214 nm): elution at 20.74 min. LC-MS: Calcd. for MH^+: 290; found: 290. ^1H NMR (400 MHz, DMSO-d_6, two rotamers, 1:1): δ 0.70-0.80 (m, 2H), 1.05-1.34 (m, 8H), 1.43-1.52 (m, 2H), 1.55-1.71 (m, 5H), 2.36 (m, 2H), 2.52 (t, J = 5 Hz, 1H), 2.62 (t, J = 5 Hz, 1H), 3.68 (t, J = 5 Hz, 1H), 3.74 (t, J = 5 Hz, 1H), 4.41 (s, 2H), 7.47 (s, 0.5H), 7.49 (s, 0.5H), 11.85 (s, br, 1H).

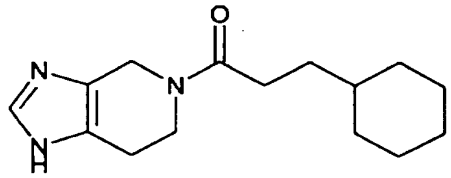
Example 3: 5-(6-Phenylhexanoyl)-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine



To a solution of carbonyldiimidazole (0.83 g, 5.12 mmol) in DCM (8 mL) 6-phenylhexanoic acid (0.98 g, 5.10 mmol) was added dropwise. The mixture was stirred at room temperature for 20 h, and then a solution of 4,5,6,7-tetrahydroimidazo[4,5-c]pyridine (5.10 mmol) in DMF (1 mL) and DCM (1 mL) was added. After stirring for four days DCM (100 mL) was added and the mixture was washed with water (15 mL) and dried ($MgSO_4$). Concentration and column chromatography (silica gel, ethyl acetate/methanol 9:1) gave 0.80 g (53%) of the title amide as an oil.

^{1}H NMR (400 MHz, DMSO-d_6, two rotamers, 1:1): δ 1.22-1.38 (m, 2H), 1.46-1.64 (m, 4H), 2.38 (m, 2H), 2.45-2.68 (m, 6H), 3.68 (t, J = 5 Hz, 1H), 3.72 (t, J = 5 Hz, 1H), 4.41 (s, 2H), 7.14-7.29 (m, 5H), 7.48 (s, 0.5H), 7.50 (s, 0.5H), 11.90 (s, br, 1H).

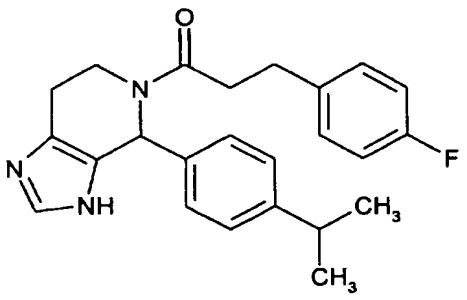
Example 4: 5-(3-Cyclohexylpropanoyl)-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine



To a solution of carbonyldiimidazole (0.83 g, 5.12 mmol) in DCM (8 mL) 3-cyclohexylpropionic acid (0.80 g, 5.10 mmol) was added dropwise. The mixture was stirred at room temperature for 20 h, and then a solution of 4,5,6,7-tetrahydroimidazo[4,5-c]pyridine (5.10 mmol) in DMF (1 mL) and DCM (1 mL) was added. After stirring for four days DCM (100 mL) was added and the mixture was washed with water (15 mL) and dried ($MgSO_4$). Concentration and column chromatography (silica gel, ethyl acetate/methanol 9:1) gave 0.66 g (50%) of the title amide as an oil.

^{1}H NMR (400 MHz, DMSO-d_6, two rotamers, 1:1): δ 0.80-0.95 (m, 2H), 1.05-1.30 (m, 4H), 1.90 (m, 2H), 1.56-1.75 (m, 5H), 2.39 (m, 2H), 2.52 (t, J = 5 Hz, 1H), 2.61 (t, J = 5 Hz, 1H), 3.69 (t, J = 5 Hz, 1H), 3.72 (t, J = 5 Hz, 1H), 4.42 (s, 2H), 7.51 (s, 0.5H), 7.53 (s, 0.5H), 11.90 (s, br, 1H).

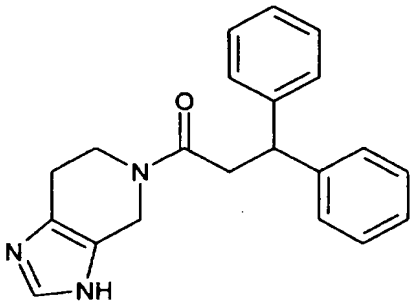
Example 5: 5-[3-(4-Fluorophenyl)propanoyl]-4-(4-isopropylphenyl)-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine



A mixture of histamine dihydrochloride (1.85 g, 10.0 mmol), water (10 mL), potassium hydroxide (1.72 g, 30.0 mmol), ethanol (25 mL) and 4-isopropylbenzaldehyde (1.62 g, 10.91 mmol) was heated to reflux for 1.5 h. Ethanol was evaporated and the residue was diluted with water (40 mL). Extraction (5 x 25 mL DCM), washing of the combined extracts (2 x 50 mL brine) and drying ($MgSO_4$) yielded 2.29 g (87%) of crude 4-(4-isopropylphenyl)-4,5,6,7-tetrahydro-imidazo[4,5-c]pyridine, which was used for the next synthetic step without further purification. This amine (0.48 g, 1.99 mmol) was dissolved in DCM (5 mL) and added to a 30 min old mixture of 3-(4-fluorophenyl)propionic acid (0.31 g, 1.84 mmol), HOBt (0.27 g, 1.20 mmol) and EDC (0.42 g, 2.19 mmol) in DCM (10 mL). After 18 h the mixture was washed with water (50 mL), dried ($MgSO_4$) and concentrated. The crude product was purified by column chromatography (silica gel, gradient elution with DCM/methanol). 0.24 g (33%) of the title amide was obtained.

HPLC (214 nm): elution at 10.21 min. LC-MS: Calcd. for MH^+: 392; found: 392. ^1H NMR (400 MHz, DMSO-d_6): δ 1.18 (d, J = 7 Hz, 6H), 2.50-2.94 (m, 7H), 3.05 (m, 1H), 3.95 (m, 1H), 6.48 (s, br, 0.7H), 6.67 (s, br, 0.3H), 6.99-7.35 (m, 8H), 7.55 (s, 1H), 11.90 (s, 1H).

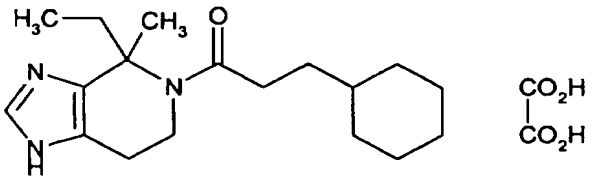
Exampl 6: 5-(3,3-Diphenylpropanoyl)-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine



To a suspension of 3,3-diphenylpropionic acid (14 mg, 0.06 mmol) and HOBt (9 mg, 0.07 mmol) in ethyl acetate (1.5 mL) a solution of EDC (12 mg, 0.06 mmol) in ethyl acetate (0.5 mL) was added. The resulting mixture was shaken for 20 min at room temperature and then 4,5,6,7-tetrahydroimidazo[4,5-c]pyridine dihydrochloride (12 mg, 0.06 mmol) and triethylamine (0.02 mL) were added. After shaking for 16 h the mixture was washed with brine (2 x 2 mL), and the organic phase was concentrated. 12 mg (60%) of the title amide was obtained.

HPLC (214 nm): elution at 8.71 min. LC-MS: Calcd. for MH^+: 332; found: 332. ^1H NMR (300 MHz, $CDCl_3$, two rotamers, 1:1): δ 2.55 (m, 2H), 3.15 (t, J = 7 Hz, 2H), 3.61 (t, J = 5 Hz, 1H), 3.80 (t, J = 5 Hz, 1H), 4.41 (s, 1H), 4.57 (s, 1H), 4.67 (m, 1H), 7.06-7.30 (m, 10H), 7.39 (s, 0.5H), 7.43 (s, 0.5H).

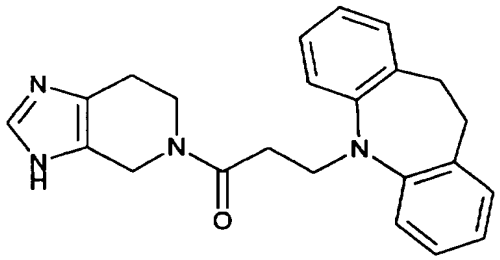
Example 7: 5-(3-Cyclohexylpropanoyl)-4-ethyl-4-methyl-4,5,6,7-tetrahydroimidazo-[4,5-c]pyridine oxalic acid salt



From histamine dihydrochloride (1.85 g, 10.0 mmol), 2-butanone (1.80 g, 25.0 mmol) and 3-cyclohexylpropanoyl chloride (2.0 g, 11.5 mmol) 0.60 g (15%) of the title oxalate was obtained using the General Procedure A.

HPLC (214 nm): elution at 19.54 min. LC-MS: Calcd. for MH^+: 304; found: 304. ^1H NMR (400 MHz, DMSO-d_6, two rotamers, 2:1): δ 0.39 (t, J = 7 Hz, 2H), 0.79-0.93 (m, 2H), 0.95 (t, J = 7 Hz, 1H), 1.05-1.29 (m, 4H), 1.39 (m, 2H), 1.49 (s, 1H), 1.59 (s, 2H), 1.60-2.10 (m, 7H), 2.15-2.50 (m, 1H), 2.60-2.99 (m, 3H), 3.28-3.49 (m, 1.3H), 3.88 (m, 0.7H), 7.69 (s, 0.3H), 8.39 (s, 0.7H).

Example 8: 5-[3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)propanoyl]-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine



Iminodibenzyl (50.0 g, 0.256 mol) was dissolved in DMF (700 mL), sodium hydride (12.3 g, 0.306 mol, 60% dispersion in oil) was slowly added in portions and the mixture was stirred at 50 °C for 2 h. Ethyl 3-bromopropionate (100 mL, 0.77 mol) was slowly added dropwise and the mixture was heated at reflux temperature overnight. The mixture was cooled and evaporated. The residue was suspended in DCM (150 mL), filtered and the solvent was evaporated. The resulting residue was purified in portions by column chromatography (silica gel, DCM) to give 5.1 g (7%) of 3-(10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)propionic acid ethyl ester.

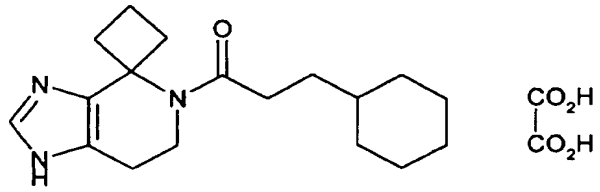
TLC: R_f = 0.69 (silica gel, DCM).

3-(10,11-Dihydro-5H-dibenzo[b,f]azepin-5-yl)propionic acid ethyl ester (1.41 g, 4.77 mmol) was dissolved in ethanol (30 mL) and a solution of sodium hydroxide (0.75 g, 18.8 mmol) in water (5 mL) was added. The mixture was stirred for 3.5 h. 1 N Hydrochloric acid (17 mL) was added and the mixture was extracted with DCM (2 x 25 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and the solvent was evaporated to give 1.18 g (92%) of 3-(10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)propionic acid.

Carbonyldiimidazole (0.33 g, 2.1 mmol) was dissolved in DCM (5 mL) and 3-(10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-1-propionic acid (0.56 g, 2.1 mmol) was added. The mixture was stirred at room temperature for 1.5 h under a nitrogen atmosphere. Simultaneously, sodium methoxide (0.8 mL of a 30% solution in water, 4.4 mmol) was added to a solution of 4,5,6,7-tetrahydroimidazo[4,5-c]pyridine dihydrochloride (0.43 g, 2.2 mmol) in methanol (5 mL). The mixture was stirred at room temperature for 1.5 h under a nitrogen atmosphere. The solvent was evaporated and the residue was stripped with DCM (6 mL). The above solution of the activated carboxylic acid was added to the residue and the reaction mixture was stirred at room temperature overnight. Water (10 mL) was added followed by DCM (50 mL) and the phases were separated. The aqueous phase was extracted with DCM (20 mL) and the combined organic phases were dried ($MgSO_4$). After evaporation of the solvent, the residue was purified by column chromatography (silica gel, 150 mL, methanol/ ethyl acetate 1:5). Evaporation of the solvent afforded 0.41 g (52%) of the title compound as a solid.

TLC: R_f = 0.28 (silica gel, methanol/ethyl acetate 1:5). LC-MS: Calcd. for MH^+: 373; found: 373. ^1H NMR (400 MHz, DMSO-d_6, two rotamers, 1:1): δ 2.49 (m, 1H), 2.60-2.72 (m, 3H), 3.07 (d, 4H), 3.47 (t, 1H), 3.86 (t, 1H), 4.08-4.20 (m, 2H), 4.22 (s, 1H), 4.62 (s, 1H), 6.90 (m, 2H), 7.01-7.16 (m, 6H), 7.40 (s, 0.5H), 7.45 (s, 0.5H).

Example 9: 5-(3-Cyclohexylpropanoyl)-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine-4-spirocyclobutane oxalic acid salt

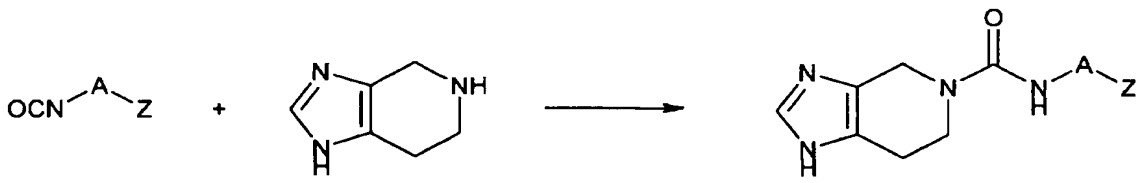


From histamine dihydrochloride (1.85 g, 10.0 mmol), cyclobutanone (1.75 g, 25.0 mmol) and 3-cyclohexylpropanoyl chloride (2.0 g, 11.5 mmol), 0.70 g (18%) of the title oxalate was obtained (General Procedure A).

HPLC (214 nm): elution at 19.40 min. LC-MS: Calcd. for MH^+: 302; found: 302. ^1H NMR (400 MHz, DMSO-d_6): δ 0.75-0.95 (m, 2H), 1.04-1.28 (m, 4H), 1.35 (q, J = 7 Hz, 2H), 1.50-2.70 (m, 11H), 3.63 (t, J = 5 Hz, 2H), 8.22 (s, br, 1H).

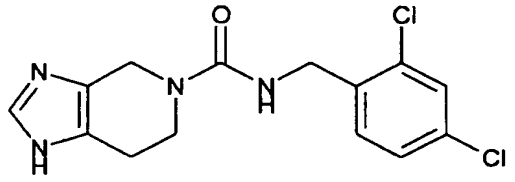
Example 10: Parallel Synthesis of Ureas

To each reactor of an array of 12 reactors, each containing a solution of 4,5,6,7-tetrahydroimidazo[4,5-c]pyridine dihydrochloride (0.07 mmol) in DMF (0.5 mL, containing 5% triethylamine) a solution of one isocyanate (0.9 equivalents) selected from 12 different isocyanates in 1,2-dichloroethane (0.2 mL) was added. The resulting mixtures were shaken overnight at room temperature. Concentration under reduced pressure gave the corresponding ureas. Using this methodology the following ureas were prepared:



Example	Z-A-	MH^+ (calcd)	MH^+ (found)
10-001	2-(2-thienyl)ethyl	277	277
10-002	3,5-dimethyl-1,2-oxazol-4-yl	262	262
10-003	1-(1-naphthyl)ethyl	321	
10-004	(2-phenylcyclopropyl)	283	283
10-005	1-(4-bromophenyl)ethyl	350	
10-006	2-(trifluoromethyl)phenyl	311	311
10-007	2-phenylethyl	271	271
10-008	4-(trifluoromethyl)phenyl	311	311
10-009	3-cyanophenyl	268	268
10-010	4-cyanophenyl	268	268
10-011	n-octyl	279	279

Example 11: 5-(2,4-Dichlorobenzylaminocarbonyl)-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine

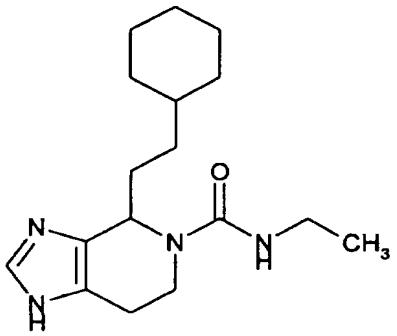


To a mixture of 4,5,6,7-tetrahydroimidazo[4,5-c]pyridine dihydrochloride (0.50 g, 2.55 mmol), ethanol (10 mL) and triethylamine (1.10 mL, 7.89 mmol), 2,4-dichlorobenzyl isocyanate (0.52 g, 2.57 mmol) was added. The resulting mixture was stirred at room temperature for 16 h and then concentrated under reduced pressure. The residue was distributed between water (20 mL) and ethyl acetate (75 mL). The organic phase was washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was triturated in diethylether (50 mL) and the

crude product was filtered off. Recrystallization from acetone (25 mL) gave 0.30 g (37%) of the title urea as a colourless solid.

HPLC (214 nm): elution at 7.97 min. LC-MS: Calcd. for MH^+: 325; found: 325. ^1H NMR (400 MHz, DMSO-d_6): δ 2.56 (s, br, 2H), 3.65 (t, J = 6 Hz, 2H), 4.29 (d, J = 6 Hz, 2H), 4.34 (s, 2H), 7.20 (s, br, 1H), 7.29 (d, J = 8 Hz, 1H), 7.39 (dd, J = 8, 1 Hz, 1H), 7.47 (s, 1H), 7.56 (d, J = 1 Hz, 1H), 11.79 (s, br, 1H).

Example 12: 4-(2-Cyclohexylethyl)-5-(ethylaminocarbonyl)-4,5,6,7-tetrahydro-imidazo[4,5-c]pyridine



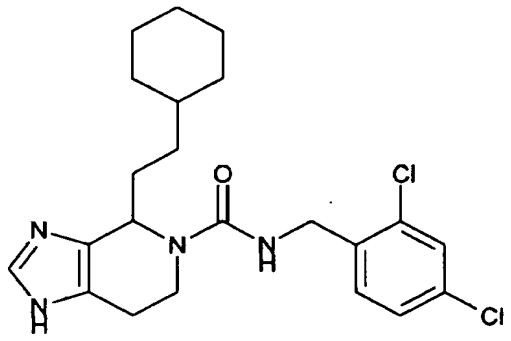
To a solution of histamine dihydrochloride (1.84 g, 10.0 mmol) in water (5 mL) methanol (40 mL) was added. To this stirred mixture an aqueous 12 N sodium hydroxide solution (4.2 mL, 50.4 mmol) and 3-(cyclohexyl)propionaldehyde (3.5 g, 25 mmol) were added. The resulting mixture was heated at reflux temperature for 20 h. Concentrated hydrochloric acid was added until pH 1 and the mixture was diluted with water (100 mL). The mixture was washed with diethyl ether (3 x 25 mL) and the aqueous solution was concentrated under reduced pressure. The residue was suspended in methanol (150 mL) and the suspension was filtered. The filtrate was concentrated under reduced pressure to give a residue which was treated with warm ethanol (75 mL). The resulting mixture was filtered and the filtrate was concentrated under reduced pressure to a volume of approximately 10 mL. Acetone (50 mL) was

added and the mixture was left for crystallization. The solid was isolated by filtration and dried under reduced pressure to give 2.4 g of a solid which was dissolved in water (10 mL). While stirring, an aqueous 1 N sodium hydroxide solution was added until pH 11-12. The resulting mixture was extracted with ethyl acetate (200 mL), the extracts were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. This afforded 1.25 g of 4-(2-cyclohexylethyl)-4,5,6,7-tetrahydroimidazo[4,5-c]-pyridine.

To a solution of the above amine (0.45 g, 1.9 mmol) in ethanol (10 mL), triethylamine (0.2 g, 1.9 mmol) and ethyl isocyanate (0.14 g, 1.9 mmol) were added. The mixture was stirred overnight at room temperature and then concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, elution with ethyl acetate/methanol 9:1). This afforded 0.14 g (24% calculated from the amine) of the title compound as a solid.

M.p. 210-212 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.85 (m, 2H), 1.00 (t, 3H), 1.05-1.45 (m, 6H), 1.50-1.75 (m, 7H), 2.35 (m, 1H), 2.55 (m, 1H), 3.03 (m, 3H), 4.10 (m, br, 1H), 4.85 (m, br, 1H), 6.38 (s, br, 1H), 7.40 (s, 1H), 11.68 (s, br, 1H).

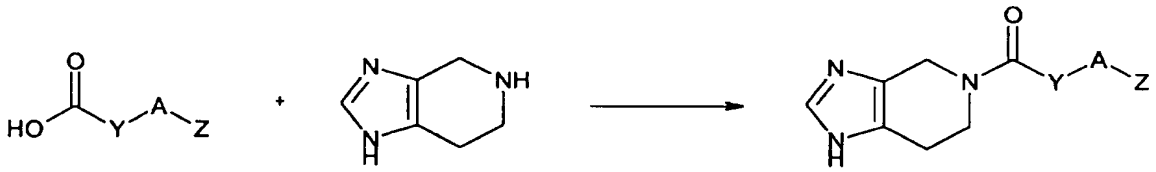
Example 13: 4-(2-Cyclohexylethyl)-5-(2,4-dichlorobenzylaminocarbonyl)-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine



To a solution of 4-(2-cyclohexylethyl)-4,5,6,7-tetrahydroimidazo[4,5-c]pyridine (0.47 g, 2.0 mmol, prepared as described in Example 13) in ethanol (10 mL), triethylamine (0.28 ml, 2.0 mmol) and 2,4-dichlorobenzyl isocyanate (0.41 g, 2.0 mmol) were added dropwise. The mixture was stirred overnight at room temperature and then concentrated under reduced pressure. The residue was re-evaporated with acetone and then dissolved in acetone (15 mL) and left for crystallization. The solid was isolated by filtration, washed with acetone and dried. This afforded 0.60 g (69%) of the title compound as a solid.

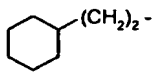
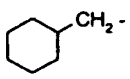
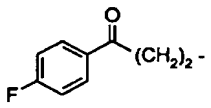
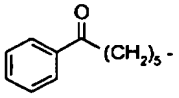
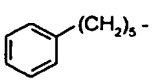
M.p. 185-187 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.85 (m, 2H), 1.05-1.45 (m, 6H), 1.52-1.70 (m, 7H), 2.42 (m, 1H), 2.60 (m, 1H), 3.09 (m, 1H), 4.18 (m, br, 1H), 4.28 (m, 2H), 4.96 (m, br, 1H), 7.10 (t, br, 1H), 7.28 (d, 1H), 7.38 (dd, 1H), 7.43 (s, 1H), 7.55 (d, 1H), 11.75 (s, br, 1H).

Example 14: Parallel Synthesis of Carboxamides.



To each reactor in an array of six, a suspension of HOBt (7.4 mg, 55 μmol) in a mixture of acetonitrile, 1,2-dichloroethane, NMP and DMSO (250 μL) was added. Then a suspension of EDC (11.5 mg, 60 μmol) in a mixture of acetonitrile, 1,2-dichloroethane, NMP and DMSO (250 μL) was added to each reactor. To each reactor a carboxylic acid (50 μmol, Z-A-Y- as listed below) dissolved in 1,2-dichloroethane (3 mL) was added and the array was shaken for 15 min. To each reactor 4,5,6,7-tetrahydroimidazo[4,5-c]pyridine (60 μmol, prepared according to General Procedure B) dissolved in a mixture of acetonitrile (250 μL) and triethylamine (210 μL, 300 μmol) was added and the array was shaken overnight. 1,2-Dichloroethane (1

mL) was added to each reactor and the array was shaken for 2 h. A 0.3 N hydrochloric acid solution (500 µL) was added to each reactor and the array was shaken for 2 h. The lower phase of each reactor was isolated with a pipette and concentrated under reduced pressure. This afforded the following six amides, identified by their MH^+ (LC-MS):

Example	Z-A-Y-	MH^+ (calcd)	MH^+ (found)
14-001		262	262
14-002		248	248
14-003		234	
14-004		302	
14-005		326	
14-006		298	298

PHARMACOLOGICAL METHODS

The ability of the compounds to interact with the histamine H3 receptor was determined by an *in vitro* binding assay. Rat cerebral cortex was homogenized in ice cold K-Hepes, 5 mM $MgCl_2$ pH 7.1 buffer. After two differential centrifugations the last pellet was resuspended in fresh Hepes buffer containing 1 mg/mL Bacitracin. Aliquots of the membrane suspension (400 mg/mL) were incubated for 60 min at 25 °C with 30 pM [^{125}I]-iodoproxifan, a known histamine H3 receptor antagonist, and the test compound at various concentrations. The incubation was stopped by dilution with ice-cold medium, followed by rapid filtration through Whatman GF/B filters

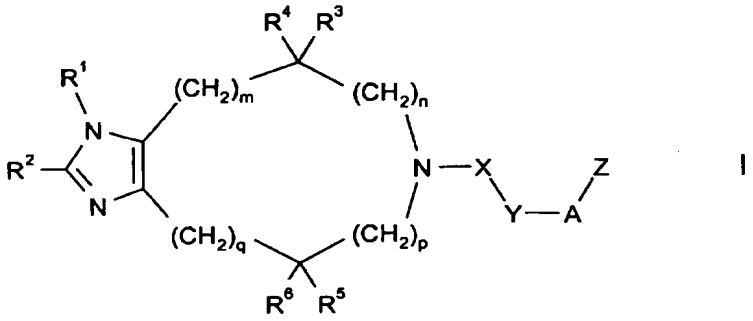
pretreated for 1 h with 0.5% polyethyleneimine. The radioactivity retained on the filters was counted using a Cobra II auto gamma counter. The radioactivity of the filters was indirectly proportional to the binding affinity of the tested compound. The results were analyzed by nonlinear regression analysis.

When tested the present compounds of the formula I showed a high binding affinity to the histamine H3 receptor.

Furthermore, in a similar way binding assays were carried out in order to determine the ability of the present compounds to interact with the histamine H1 receptor (reference compound [^{125}I]-pyrilamine) and the histamine H2 receptor (reference compound [^{125}I]-aminopotentidine), respectively. These assays showed that the present compounds do not show a high affinity for these receptors and hence are very specific to the histamine H3 receptor.

CLAIMS

1. A compound of the general formula I



I

wherein

R^1 is hydrogen or a functional group which can be converted to hydrogen *in vivo*;

R^2 is hydrogen, C_{1-6}-alkyl, halogen, cyano, trifluoromethyl, hydroxy or $-NR^7R^8$

wherein R^7 and R^8 independently are

hydrogen;

C_{1-6}-alkyl optionally substituted with aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroarylamino or C_{3-8}-cycloalkyl which are optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

aryl optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

heteroaryl optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

aroyl optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

heteroaroyl optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

arylsulfonyl optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

heteroarylsulfonyl optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino; or

C_{1-6}-alkylsulfonyl optionally substituted with C_{3-6}-cycloalkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino; or

R^7 and R^8, together with the nitrogen atom to which they are connected, form a 3 to 8 membered, saturated or unsaturated, carbocyclic or heterocyclic ring optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

R^3, R^4, R^5 and R^6 independently are

hydrogen; carboxy; C_{1-6}-alkoxycarbonyl; -CO-NR^7R^8 wherein R^7 and R^8 are as defined above; cyano; or halogen;

C_{3-8}-cycloalkyl optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

C_{1-6}-alkyl optionally substituted with

C_{1-6}-alkoxy; C_{1-6}-alkylthio; hydroxy; cyano; halogen; trifluoromethyl; carboxy; C_{1-6}-alkoxycarbonyl; or -CO-NR^7R^8 wherein R^7 and R^8 are as defined above; or C_{3-8}-cycloalkyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino which are optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

C_{2-6}-alkenyl optionally substituted with

C_{1-6}-alkoxy; C_{1-6}-alkylthio; hydroxy; cyano; halogen; trifluoromethyl; carboxy; C_{1-6}-alkoxycarbonyl; or -CO-NR^7R^8 wherein R^7 and R^8 are as defined above; or C_{3-8}-cycloalkyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino which are optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

C_{2-6}-alkynyl optionally substituted with

C_{1-6}-alkoxy; C_{1-6}-alkylthio; hydroxy; cyano; halogen; trifluoromethyl; carboxy; C_{1-6}-alkoxycarbonyl; or -CO-NR^7R^8 wherein R^7 and R^8 are as defined above; or C_{3-8}-cycloalkyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino which are optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy,

C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino; or

aryl optionally substituted with halogen, cyano, nitro, C_{1-6}-alkyl, C_{1-6}-alkoxy, hydroxy, trifluoromethyl, aryl, heteroaryl, aryloxy, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroarylamino or -CO-NR^7R^8 wherein R^7 and R^8 are as defined above ; or

R^3 and R^4, together with the carbon atom to which they are connected, and/or R^5 and R^6 together with the carbon atom to which they are connected, form a 3 to 8 membered, saturated or unsaturated, carbocyclic or heterocyclic ring optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

m, n, p and q independently are 0, 1 or 2;

X is a valence bond, $-CH_2-$, -C(=O)-, -C(=S)-, -S(=O)-, $-S(=O)_2-$, -C(=N-CN)-, $-C(=CH-NO_2)-$, $-C[=C(CN)_2]-$, -C(=CH-CN)-, or $-C(=NR^7)-$ wherein R^7 is as defined above;

Y is a valence bond, -O- or $-N(R^7)-$ wherein R^7 is as defined above;

A is a valence bond, C_{1-6}-alkylene, C_{2-6}-alkenylene, C_{2-6}-alkynylene, C_{3-6}-cycloalkylene or phenylene; or

when Y is $-N(R^7)-$, A may together with R^7 form a 3 to 8 membered, saturated or unsaturated, carbocyclic or heterocyclic ring optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino; and

Z is $-R^9$, $-OR^9$, $-SR^9$, $-NR^9R^{10}$, $-CHR^9R^{10}$ or $=CR^9R^{10}$

wherein R^9 and R^{10} independently are

hydrogen;

C_{1-6}-alkyl optionally substituted with aryl, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, heteroaryl or C_{3-8}-cycloalkyl which are optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, hydroxy, amino, halogen, cyano or trifluoromethyl;

C_{2-6}-alkenyl optionally substituted with aryl, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, heteroaryl or C_{3-8}-cycloalkyl which are optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, hydroxy, amino, halogen, cyano or trifluoromethyl;

C_{2-6}-alkynyl optionally substituted with aryl, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, heteroaryl or C_{3-8}-cycloalkyl which are optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, hydroxy, amino, halogen, cyano or trifluoromethyl;

aryl optionally substituted with aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano or trifluoromethyl;

C_{3-15}-cycloalkyl optionally substituted with aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano or trifluoromethyl;

aroyl optionally substituted with aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano or trifluoromethyl; or

heteroaryl optionally substituted with aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano or trifluoromethyl; or

R^9 and R^{10} are joined by one or more bridging linkers such as a valence bond, C_{1-4}-alkylene, C_{2-4}-alkenylene, -O-, -S-, -N(R^7)-, -C(=O)-, -S(=O)-, -S(=O)$_2$-, -C(R^7R^8)-, phenylene, biphenylene, -O-C_{1-4}-alkylene, -S-C_{1-4}-alkylene, -N(R^7)-C_{1-4}-alkylene, -N=C_{1-4}-alkylene, -O-C_{2-4}-alkenylene, -S-C_{2-4}-alkenylene, or -N(R^7)-C_{2-4}-alkenylene, to form a mono-, bi- or polycyclic ring system; or

when Y is -N(R^7)-, R^9 or R^{10} may together with R^7 form a 3 to 8 membered, saturated or unsaturated, carbocyclic or heterocyclic ring optionally substituted with aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano or trifluoromethyl;

with the provisos that

when X is -CS-, $R^1 = R^2 = R^5 = R^6$ = hydrogen, m = n = p = 0 and q = 1, the group -Y-A-Z must not start with the radical -NH-;

when the group -X-Y-A-Z starts with the radical -CH_2-, $R^1 = R^2 = R^6$ = hydrogen, m = n = p = 0 and q = 1, R^5 must not be carboxy or aminocarbonyl;

when X is -CO-, the group -Y-A-Z starts with the radical -NH-, $R^1 = R^2 = R^6$ = hydrogen, m = n = p = 0 and q = 1, the remainder of the group -Y-A-Z must not be hydrogen, unsubstituted or C_{1-6}-alkoxy substituted phenyl, unsubstituted C_{3-8}-cycloalkyl or unsubstituted C_{1-6}-alkyl;

when X is -CO-, the group -Y-A-Z starts with the radical -O-, $R^1 = R^2 = R^6$ = hydrogen, m = n = p = 0 and q = 1, R^5 must not be carboxy, aminocarbonyl or hydrogen;

when -X is -CO-, the group -Y-A-Z starts with the radical -CH<, $R^1 = R^2 = R^3 = R^4 = R^6$ = hydrogen, m = n = p = 0 and q = 1, R^5 must not be hydroxymethyl, C_{1-6}-alkoxycarbonyl or carboxy; and

when X is -CO-, the group -Y-A-Z is 4-methoxyphenyl, $R^1 = R^2 = R^3 = R^4 = R^6$ = hydrogen, m = n = p = 0 and q = 1, R^5 must not be carboxy;

and a pharmaceutically acceptable salt thereof or any optical isomer thereof or mixture of optical isomers, including a racemic mixture, or any tautomeric form.

2. A compound according to claim 1 wherein X is -C(=O)-; Y is a valence bond; A is a valence bond or C_{1-8}-alkylene; and Z is $-R^9$ or $-CHR^9R^{10}$.

3. A compound according to claim 2 wherein $R^1 = R^2$ = hydrogen; and m = n = p = 0 and q = 1.

4. A compound according to claim 3 wherein Z is $-R^9$ in which R^9 is

aryl, C_{3-15}-cycloalkyl, aroyl or heteroaryl which are optionally substituted with aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano or trifluoromethyl.

5. A compound according to claim 3 wherein Z is $-CHR^9R^{10}$ in which R^9 and R^{10} independently are

hydrogen; or

aryl, C_{3-15}-cycloalkyl, aroyl or heteroaryl which are optionally substituted with aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano or trifluoromethyl.

6. A compound according to claim 1 wherein $R^1 = R^2$ = hydrogen; m = n = p = 0 and q = 1; X is -C(=O)-; Y is a valence bond; A is a valence bond or C_{1-8}-alkylene; and Z is $-NR^9R^{10}$ or $-CHR^9R^{10}$ in which R^9 and R^{10} independently represent

hydrogen; or

aryl, C_{3-15}-cycloalkyl, aroyl or heteroaryl which are optionally substituted with aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano or trifluoromethyl;

which are joined with a C_{1-4}-alkylene group to form a cyclic ring system.

7. A compound according to claim 1 wherein $R^1 = R^2$ = hydrogen; m = n = p = 0 and q = 1; X is -C(=O)-; Y is -NH-; A is a valence bond, C_{1-8}-alkylene or C_{3-8}-cycloalkylene; and

Z is $-R^9$ in which R^9 is

C_{1-6}-alkyl optionally substituted with aryl, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, heteroaryl or C_{3-8}-cycloalkyl which are optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, hydroxy, amino, halogen, cyano or trifluoromethyl;

aryl optionally substituted with aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano or trifluoromethyl;

C_{3-15}-cycloalkyl optionally substituted with aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano or trifluoromethyl; or

heteroaryl optionally substituted with aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano or trifluoromethyl; or

Z is $-CHR^9R^{10}$ in which R^9 and R^{10} independently are

hydrogen;

C_{1-6}-alkyl optionally substituted with aryl, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, heteroaryl or C_{3-8}-cycloalkyl which are optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, aryl-C_{1-6}- alkyl, heteroaryl-C_{1-6}-alkyl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, hydroxy, amino, halogen, cyano or trifluoromethyl;

aryl optionally substituted with aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano or trifluoromethyl;

C_{3-15}-cycloalkyl optionally substituted with aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano or trifluoromethyl; or

heteroaryl optionally substituted with aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano or trifluoromethyl.

8. A compound according to any one of the preceding claims wherein R^3 and R^4 independently are

hydrogen;

C_{3-8}-cycloalkyl optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

C_{1-6}-alkyl optionally substituted by C_{3-8}-cycloalkyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino which are optionally substituted with

C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

aryl optionally substituted with halogen, cyano, nitro, C_{1-6}-alkyl, C_{1-6}-alkoxy, hydroxy, trifluoromethyl, aryl, heteroaryl, aryloxy, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroarylamino or -CO-NR^7R^8 wherein R^7 and R^8 are as defined above; or

R^3 and R^4, together with the carbon atom to which they are connected, and/or R^5 and R^6 together with the carbon atom to which they are connected, form a C_{3-8}-cycloalkyl ring optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino.

9. A compound according to any one of the claims 1 to 8 wherein R^5 and R^6 are both hydrogen.

10. A compound according to any one of the claims 1 to 9 wherein m = n = p = 0 and q = 1, and R^3 and R^4 are both hydrogen or are both C_{1-6}-alkyl or R^3 and R^4, together with the carbon atom to which they are connected, form a C_{3-8}-cycloalkyl ring.

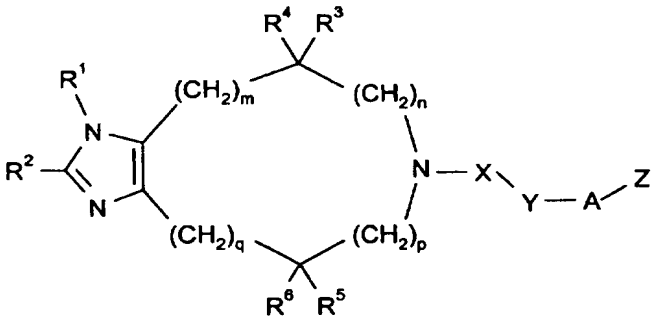
11. A compound according to any one of the claims 1 to 10 wherein R^3, R^4, R^5 and R^6 are hydrogen.

12. A compound according to any one of the claims 1 to 11 for use as a medicament.

13. A pharmaceutical composition comprising, as an active ingredient, at least one compound according to any one of the claims 1 to 11 together with one or more pharmaceutically acceptable carriers or diluents.

14. A pharmaceutical composition according to claim 13 in unit dosage form, comprising from about 0.05 mg to about 1000 mg, preferably from about 0.1 mg to about 500 mg and especially preferred from about 0.5 mg to about 200 mg of the compound according to any one of the claims 1 to 11.

15. Use of a compound of the general formula I'



I'

wherein

R^1 is hydrogen or a functional group which can be converted to hydrogen *in vivo*;

R^2 is hydrogen, C_{1-6}-alkyl, halogen, cyano, trifluoromethyl, hydroxy or $-NR^7R^8$

wherein R^7 and R^8 independently are

hydrogen;

C_{1-6}-alkyl optionally substituted with aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroarylamino or C_{3-8}-cycloalkyl which are optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

aryl optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

heteroaryl optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

aroyl optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

heteroaroyl optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

arylsulfonyl optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

heteroarylsulfonyl optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino; or

C_{1-6}-alkylsulfonyl optionally substituted with C_{3-8}-cycloalkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino; or

R^7 and R^8, together with the nitrogen atom to which they are connected, form a 3 to 8 membered, saturated or unsaturated, carbocyclic or heterocyclic ring optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

R^3, R^4, R^5 and R^6 independently are

hydrogen; carboxy; C_{1-6}-alkoxycarbonyl; -CO-NR^7R^8 wherein R^7 and R^8 are as defined above; cyano; or halogen;

C_{3-8}-cycloalkyl optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

C_{1-6}-alkyl optionally substituted with

C_{1-6}-alkoxy; C_{1-6}-alkylthio; hydroxy; cyano; halogen; trifluoromethyl; carboxy; C_{1-6}-alkoxycarbonyl; or -CO-NR^7R^8 wherein R^7 and R^8 are as defined above; or C_{3-8}-cycloalkyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino which are optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

C_{2-6}-alkenyl optionally substituted with

C_{1-6}-alkoxy; C_{1-6}-alkylthio; hydroxy; cyano; halogen; trifluoromethyl; carboxy; C_{1-6}-alkoxycarbonyl; or -CO-NR^7R^8 wherein R^7 and R^8 are as defined above; or

C_{3-8}-cycloalkyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino which are optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

C_{2-6}-alkynyl optionally substituted with

C_{1-6}-alkoxy; C_{1-6}-alkylthio; hydroxy; cyano; halogen; trifluoromethyl; carboxy; C_{1-6}-alkoxycarbonyl; or -CO-NR^7R^8 wherein R^7 and R^8 are as defined above; or C_{3-8}-cycloalkyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino which are optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino; or

aryl optionally substituted with halogen, cyano, nitro, C_{1-6}-alkyl, C_{1-6}-alkoxy, hydroxy, trifluoromethyl, aryl, heteroaryl, aryloxy, aroyl, heteroaroyl, arylsulfonyl, arylamino, heteroarylamino or -CO-NR^7R^8 wherein R^7 and R^8 are as defined above ; or

R^3 and R^4, together with the carbon atom to which they are connected, and/or R^5 and R^6 together with the carbon atom to which they are connected, form a 3 to 8 membered, saturated or unsaturated, carbocyclic or heterocyclic ring optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino;

m, n, p and q independently are 0, 1 or 2;

X is a valence bond, -CH_2-, -C(=O)-, -C(=S)-, -S(=O)-, -$S(=O)_2$-, -C(=N-CN)-, -$C(=CH-NO_2)$-, -$C[=C(CN)_2]$-, -C(=CH-CN)-, or -$C(=NR^7)$- wherein R^7 is as defined above;

Y is a valence bond, -O- or -N(R^7)- wherein R^7 is as defined above;

A is a valence bond, C_{1-8}-alkylene, C_{2-8}-alkenylene, C_{2-8}-alkynylene, C_{3-8}-cycloalkylene or phenylene; or

when Y is -N(R^7)-, A may together with R^7 form a 3 to 8 membered, saturated or unsaturated, carbocyclic or heterocyclic ring optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano, trifluoromethyl, aryl, heteroaryl, aroyl, heteroaroyl, arylsulfonyl, arylamino or heteroarylamino; and

Z is $-R^9$, $-OR^9$, $-SR^9$, $-NR^9R^{10}$, $-CHR^9R^{10}$ or $=CR^9R^{10}$

wherein R^9 and R^{10} independently are

hydrogen;

C_{1-6}-alkyl optionally substituted with aryl, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, heteroaryl or C_{3-8}-cycloalkyl which are optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, hydroxy, amino, halogen, cyano or trifluoromethyl;

C_{2-6}-alkenyl optionally substituted with aryl, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, heteroaryl or C_{3-8}-cycloalkyl which are optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl,

C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, hydroxy, amino, halogen, cyano or trifluoromethyl;

C_{2-6}-alkynyl optionally substituted with aryl, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, heteroaryl or C_{3-8}-cycloalkyl which are optionally substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, hydroxy, amino, halogen, cyano or trifluoromethyl;

aryl optionally substituted with aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano or trifluoromethyl;

C_{3-15}-cycloalkyl optionally substituted with aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano or trifluoromethyl;

aroyl optionally substituted with aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano or trifluoromethyl; or

heteroaryl optionally substituted with aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino, aroyl, het roaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano or trifluoromethyl; or

R^9 and R^{10} are joined by one or more bridging linkers such as a valence bond, C_{1-4}-alkylene, C_{2-4}-alkenylene, -O-, -S-, -N(R^7)-, -C(=O)-, -S(=O)-, -S(=O)$_2$-, -C(R^7R^8)-, phenylene, biphenylene, -O-C_{1-4}-alkylene, -S-C_{1-4}-alkylene, -N(R^7)-C_{1-4}-alkylene, -N=C_{1-4}-alkylene, -O-C_{2-4}-alkenylene, -S-C_{2-4}-alkenylene, or -N(R^7)-C_{2-4}-alkenylene, to form a mono-, bi- or polycyclic ring system; or

when Y is -N(R^7)-, R^9 or R^{10} may together with R^7 form a 3 to 8 membered, saturated or unsaturated, carbocyclic or heterocyclic ring optionally substituted with aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, aryl, heteroaryl, nitro, arylamino, heteroarylamino, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, C_{1-6}-alkylsulfonyl, sulfonylamino, arylthio, heteroarylthio, aryloxy, acylamino, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, amino, halogen, cyano or trifluoromethyl;

or a pharmaceutically acceptable salt thereof or any optical isomer thereof or mixture of optical isomers, including a racemic mixture, or any tautomeric form for the preparation of a medicament for the treatment of disorders related to the histamine H3 receptor.

16. Use of a compound as defined in claim 15 for the preparation of a medicament having histamine H3 antagonistic activity.

17. Use of a compound as defined in claim 15 for the preparation of a medicament for the treatment and/or prevention of eating disorders such as bulimia or anorexia.

18. Use of a compound as defined in claim 15 for the preparation of a medicament for the treatment and/or prevention of obesity.

19. Use of a compound as defined in claim 15 for the preparation of a medicament for use in the treatment of disorders related to the serotonin-3 receptor (5-HT3), such as for use in the treatment of emesis.

20. Use of a compound as defined in claim 15 for the preparation of a medicament for use in the treatment of disorders related to the vanilloid receptor, such as for use in the treatment of pain, neurogenic inflammation or obesity.

21. Use of a compound as defined in claim 15 for the preparation of a medicament for use in the treatment of disorders related to the alpha-2 adrenergic receptor, such as for use as a sleep inducing agent.

22. A method for the treatment of disorders related to the histamine H3 receptor the method comprising administering to a subject in need thereof an effective amount of a compound as defined in claim 15 or a pharmaceutical composition comprising the compound.

23. The method according to claim 22 wherein the effective amount of the compound as defined in claim 15 is in the range of from about 0.05 mg to about 1000 mg, preferably from about 0.1 mg to about 500 mg and especially preferred from about 0.5 mg to about 200 mg per day.

24. Any novel feature or combination of features as described herein.

ABSTRACT

A novel class of substituted imidazole derivatives, methods for their preparation, pharmaceutical compositions comprising them and use thereof in the treatment of disorders related to the histamine H3 receptor. More particularly, the compounds possess histamine H3 receptor antagonistic activity and are thus useful in the treatment of disorders in which a histamine H3 receptor blockade is beneficial.